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A.M.A. SESSION — St. Louis — MAY 15-19, 1939

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RELATION OF DRUG THERAPY TO NEUTROPENIC STATES

CHAIRMAN'S ADDRESS

ROY R. KRACKE, M.D.

EMORY UNIVERSITY, GA.

In 1931 the first evidence was presented that the disease agranulocytosis was caused by the administration of certain drugs.[1] Since that time there have accumulated a large amount of confirmatory data and reports of experiments from over the world that this concept is correct. The purpose of this paper is to summarize this evidence and to make further suggestions concerning the use of some of these drugs, particularly since new preparations are being introduced constantly and at least one of them (sulfanilamide) can be definitely added to the list of offenders.

AMINOPYRINE

The incrimination of aminopyrine in the production of neutropenic diseases is based, first, on geographic studies which show that the incidence of the disease closely parallels the use of the drug; second, on the fact that the incidence is higher for the groups of the population that are the most habitual users of the drug; third, on the collection of records showing that in a large majority of patients with agranulocytosis the disease has followed the administration of the drug, and, fourth, on the administration of aminopyrine to an occasional patient who has recovered, with consequent reproduction of the disease. The fourth type of evidence adds conclusive proof that this drug is capable of producing agranulocytosis in an occasional person.

In 1935 Kracke and Parker [2] summarized the relationship between agranulocytosis and aminopyrine and collected 153 reported cases of agranulocytosis which had followed the use of aminopyrine. In 1937 Plum,[3] in the most comprehensive review of the disease that has yet appeared, collected 267 cases in which it had apparently followed the use of aminopyrine.

The evidence incriminating this drug has been supported by clinical experiments in which patients who have recovered have been given small doses of the preparation and the disease reproduced in them. Such experiments have been carried out by Madison and Squier,[4] Benjamin and Biederman,[5] Sturgis and Isaacs,[6] Plum [3] and others, and all of them demonstrated that the occasional person who has been fortunate enough to recover from the disease can have it induced a second time by the administration of even a small amount of aminopyrine. Furthermore, in nearly every case in which the disease has developed while the patient was being hospitalized for another condition, it followed the administration of this drug.

Recent clinical experiments of importance are those of Dameshek and Colmes,[7] who studied four patients who had recovered from the disease. The first patient was given 10 grains (0.6 Gm.) of aminopyrine by mouth, had marked leukopenia and recovered. The second patient was given 10 grains of aminopyrine every two hours for five doses; there was no immediate change in the blood cells, but an attack of agranulocytosis occurred two weeks later. Another patient, after being given 10 grains of aminopyrine every three hours for three doses, presented marked leukopenia. These patients were tested by scratch, intradermal and patch tests, an aqueous solution of the drug being used, but the results were negative. However, when the same solution was mixed with blood serum and permitted to age under refrigeration, the tests with this preparation were positive. Furthermore, a second attack of the disease was produced by the intradermal injection of as little as 0.6 grain (0.04 Gm.) of this "serumized aminopyrine."

This evidence all indicates that the occasional person who acquires the disease after the administration of this drug does so on the basis of a hypersensitivity to it. Therefore it seems reasonable that the patient is allergic to the action of aminopyrine and that the amount of the drug given plays little part in the production of the disease.

This is further indicated by the report of Madison and Squier,[4] who gave a single dose of aminopyrine to each of two patients, with marked depletion of the granulocytes, and the report of Benjamin and Biederman,[5] who produced marked leukopenia with one dose of the drug.

An important and conclusive link in the incrimination of this drug is found in the recent report of Plum,[3] in which he showed the incidence of agranulocytosis correlated with the use and sale of aminopyrine in

Read before the Section on Pathology and Physiology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 16, 1938

1. Kracke, R. R.: The Experimental Production of Agranulocytosis, Am. J. Clin. Path. **2**: 11 (Jan.) 1932.
2. Kracke, R. R., and Parker, F. P.: The Relationship of Drug Therapy to Agranulocytosis, J. A. M. A. **105**: 960 (Sept. 21) 1935.
3. Plum, P.: Clinical and Experimental Investigations in Agranulocytosis with Special Reference to the Etiology, translated by Hans Andersen, London, H. K. Lewis & Co., Ltd., 1937.
4. Madison, F. W., and Squier, T. L.: The Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. **102**: 755 (March 10) 1934.
5. Benjamin, J. E., and Biederman, J. B.: Agranulocytic Leukopenia: Report of a Case Successfully Treated with X-Rays; Effect of Aminopyrine, J. A. M. A. **103**: 161 (July 21) 1934.
6. Sturgis, C. C., and Isaacs, Raphael: Observations Concerning Etiology of Agranulocytosis, Tr. A. Am. Physicians **49**: 328, 1934.
7. Dameshek, William, and Colmes, Abraham: The Effect of Drugs in the Production of Agranulocytosis with Particular Reference to Amidopyrine Hypersensitivity, J. Clin. Investigation **15**: 85 (Jan.) 1936.

Denmark through the years from 1925 to 1936, as summarized in the accompanying chart.

From this chart it will be seen that the consumption of aminopyrine in Denmark before the disease made its appearance was practically nil and that there was a gradual increase in the use of aminopyrine paralleling the increasing number of cases of agranulocytosis, the peak being reached in 1934. At that time the use of the drug was practically abandoned, and the disease disappeared. Plum [3] concluded from his studies that aminopyrine was by far the most frequent cause of agranulocytosis in Denmark.

Many workers have endeavored to reproduce agranulocytosis in lower animals by the injection of aminopyrine and related compounds, but their experiments in general have been unsuccessful. My associates and I have injected aminopyrine in solution into rabbits, guinea pigs, dogs and rats and have fed the drug by mouth to a large number of animals but have been unable to produce a marked depression of the leukocytes in any of them.

Stenn [8] has administered the drug by various routes to a total of 120 animals, including rabbits, guinea

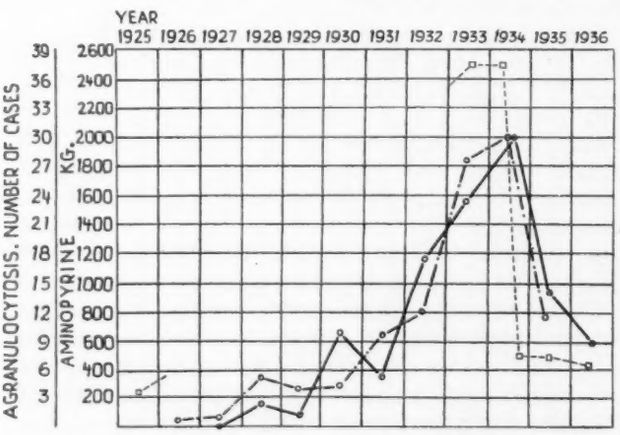

Chart showing practically complete disappearance of agranulocytosis from Denmark after the importation of aminopyrine was prohibited (from Plum [3]). The solid line indicates the number of cases of agranulocytosis, the dots and dashes the sale of aminopyrine from importing firms and the broken line the estimated total consumption of aminopyrine.

pigs and monkeys, but with no success in producing depression of the leukocytes. On the other hand, we have submitted the drug to an oxidation process such as conceivably might occur in the intestinal tract and have produced moderate leukopenia, but in only an occasional animal. Madison and Squier [4] reported a marked depression of the leukocytes in only one rabbit of a total of eleven fed tablets of allylisopropylbarbituric acid and aminopyrine (allonal). Miller and Rhoads,[9] using a total of fifteen dogs, gave some of them aminopyrine by mouth in conjunction with a blacktongue-producing diet and were able to produce acute stomatitis and anemia before these conditions would have developed from an inadequate diet alone, and they found a suppression of maturation of the bone marrow elements.

Climenko [10] measured the amount of response of the leukocytes in rabbits after injection of sodium nucleinate and measured it again after the animals had been given aminopyrine and dinitrophenol. The height of the response was much less in the drug-fed animals, and study of the bone marrow showed myeloid hyperplasia followed by suppression of maturation, with some degeneration and necrosis and finally aplasia. This would indicate that the bone marrow in its entirety has to be damaged rather severely before evidence of depression is seen in the peripheral blood and that the marrow has a large reserve power.

Many experiments have been done in an effort to show the effect of aminopyrine on groups of normal and abnormal human beings. For example, Rawls [11] observed the development of agranulocytosis in four of 400 patients who were receiving aminopyrine in the treatment of arthritis. Davis and Frissell [12] gave 30 grains (2 Gm.) of aminopyrine daily to thirty-two patients for from two weeks to three months with no change in the leukocyte count. In this connection Plum [3] said "It has been well demonstrated that amidopyrine given to large groups of people is not followed by the development of the disease unless one of them happens to have the necessary sensitivity to the drug" and "It has been demonstrated that other drugs have no effect on the blood of persons sensitive to amidopyrine and that amidopyrine has no effect on the blood of nonsensitive persons."

There is now general agreement that aminopyrine is dangerous and that its use should be drastically restricted. Thus, Bie [13] of Copenhagen said "If we want to avoid the risk of producing agranulocytosis, the only way is not to use amidopyrine at all," while Witts [14] of England declared "Amidopyrine is a dangerous drug and all remedies which contain it should be clearly branded as dangerous drugs with the word 'amidopyrine' and not some alias" and Comroe [15] of Pennsylvania suggested "that this drug be dropped from the pharmaceutical armamentarium."

DINITROPHENOL

Dinitrophenol, which has been used mainly in the treatment of obesity, can definitely be included in the list of drugs that produce neutropenic diseases. Hoffman, Butt and Hickey,[16] Davidson and Shapiro,[17] Dameshek and Gargill,[18] Silver [19] and Frank [20] have reported a total of seven cases, two of which were fatal. In addition, the drug is known to produce cataracts in an occasional patient, so that its use in the last two years has been curtailed to a considerable degree and reports of agranulocytosis following its use have become more infrequent.

ARSPHENAMINE

Plum has reviewed the literature of the neutropenic diseases following the administration of arsphenamine with and without preparations of bismuth. In fourteen

8. Stenn, Fred: The Etiologic Relationship of Amidopyrine to Agranulocytosis, J. Lab. & Clin. Med. **20**: 1150 (Aug.) 1935.
9. Miller, D. K., and Rhoads, C. P.: The Effect of Diet on the Susceptibility of the Canine Hematopoietic Function to Damage by Amidopyrine, J. Exper. Med. **66**: 367 (Sept.) 1937.
10. Climenko, D. R.: The Modification of the Hematopoietic Function in the Rabbit by Certain Cyclic Compounds, J. Lab. & Clin. Med. **21**: 913 (Jan.) 1936.
11. Rawls, W. B.: The Effect of Amidopyrine upon the Red, White and Polymorphonuclear Blood Cells of a Series of One Hundred Patients, Am. J. M. Sc. **192**: 175 (Aug.) 1936.
12. Davis, J. S., and Frissell, L. F.: Amidopyrine Hypersensitivity, J. Lab. & Clin. Med. **23**: 107 (Nov.) 1937.
13. Bie, V.: Agranulocytosis, Nord. med. tidskr. **11**: 208, (Feb. 8) 1936. Quoted by Plum.[3]
14. Witts, L. J.: Effect of Toxic Substances on the Blood-Forming Organs, Brit. M. J. **2**: 211 (Aug. 1) 1936.
15. Comroe, B. I.: Drugs as Etiologic Factor in Agranulocytic Angina, Ann. Dent. **3**: 17 (March) 1936.
16. Hoffman, A. M.; Butt, E. M., and Hickey, N. G.: Neutropenia Following Aminopyrine: Preliminary Report, J. A. M. A. **102**: 1213 (April 14) 1934.
17. Davidson, E. N., and Shapiro, Matthew: Neutropenia Following Dinitrophenol with Improvement After Pentnucleotide and Leukocyte Cream, J. A. M. A. **103**: 480 (Aug. 18) 1934.
18. Dameshek, William, and Gargill, S. L.: Studies in Agranulocytosis: Report of Two Cases of Agranulocytosis Following the Use of Dinitrophenol, New England J. Med. **21**: 440 (Sept. 6) 1934.
19. Silver, Solomon: A New Danger in Dinitrophenol Therapy: Agranulocytosis with Fatal Outcome, J. A. M. A. **103**: 1058 (Oct. 6) 1934.
20. Frank, Ira: Granulocytic Angina: Report of Three Cases with Two Fatalities, Arch. Otolaryng. **23**: 310 (March) 1936.

cases the hematologic defect was limited to the granulocytes and there was no anemia or sign of hemorrhagic diathesis. Furthermore, occasional reports, such as that of Blew,[21] indicate that this drug does produce in an occasional person a hematologic and clinical syndrome that is indistinguishable from agranulocytosis. He reported this syndrome in three young white males, one of whom had received sixty-eight injections of neoarsphenamine, another a large number and a third only three.

The depressing effect of organic arsenical compounds on the bone marrow elements has long been recognized, but it should be borne in mind that these drugs are capable of producing hematologic defects limited to the granulocytes and therefore agranulocytosis.

COMPOUNDS SIMILAR TO AMINOPYRINE

As soon as the dangers of aminopyrine had become generally recognized it was to be expected that certain pharmaceutical companies would produce similar compounds in which very slight chemical changes were made so that the therapeutic effect would be as nearly identical with that of aminopyrine as possible and yet the preparation could be given another name. An example of such compounds is that marketed under the name of novaldin. This preparation has the same chemical formula as aminopyrine except that one of the methyl groups attached to the amino nitrogen is replaced by the sodium salt of methyl sulfonic acid.

Agranulocytosis following the administration of this preparation has been reported by Klumpp[22] and by Benjamin and Biederman.[23] Ironically enough, Klumpp's patient took this preparation because his physician warned him against the dangers of aminopyrine. Benjamin and Biederman gave 10 grains of novaldin to a patient who had recovered from agranulocytosis which had followed the use of aminopyrine. Within eight hours the clinical symptoms of the disease developed, including a leukocyte count of 2,800 per cubic millimeter. This experiment is important because it indicates that the person who is sensitive to aminopyrine is also sensitive to novaldin, though this was to be expected because the two preparations are so nearly identical.

SULFANILAMIDE

This remarkable drug, which has proved to be of so much value in the treatment of beta streptococcus infections, is not without its dangers to the blood. These dangers include the development of methemoglobinemia and cyanosis, acute hemolytic anemia and agranulocytosis. I have found eleven cases of agranulocytosis in which the disease apparently followed the administration of sulfanilamide. These are summarized in table 1.

It will be noted that these cases have all been reported since April 1937 and that over half of the patients were young adults. In every instance a large amount of drug was administered (from 40 to 50 Gm.) before the disease made its appearance. This indicates that the mechanism of granulopoietic depression may be different from that following the administration of a single dose of aminopyrine. In practically all these cases the leukocyte count fell to extremely low levels, with complete disappearance of the neutrophils. The usual clinical symptoms followed, and death occurred in nine of the eleven cases. In nearly all of them the administration of other leukocyte-depressing drugs could have been eliminated.

Therefore, on the basis of these reports, sulfanilamide can be added to the list of drugs that are capable of producing agranulocytosis. Furthermore, it should be borne in mind that because of the increasing use of this drug there will probably be an increasing number of cases in which the disease will follow its administration. This is especially true because the preparation can be purchased by the public in drug stores and used widely without medical supervision. Unfortunately in this connection it is similar to aminopyrine. It is reasonable to assume that the market will shortly become flooded with patented remedies containing this drug and that the dangers of agranulocytosis will become more accentuated.

I have observed two patients in whom the disease developed after the administration of sulfanilamide.

TABLE 1.—*Agranulocytosis Following the Administration of Sulfanilamide*

Date	Author	Age	Sex	Race	Amount of Drug	Leukocyte Count	Outcome	Other Drugs
April 1937	Plumer, H. E.: New England J. Med **216**: 711, 1937	54	♀	W	Daily dose 33 days	W.B.C. 400 No granulocytes	Death	None
June 1937	Borst, J. G. G.: Lancet **1**: 1519, 1937.....	61	♀	W	45 Gm. 18 days	W.B.C. 900 Granulocytes 1%	Death	Dilute hydrochloric acid; castor oil
July 1937	Young, C. J.: Brit. Med. J. **2**: 105, 1937.....	53	♂	W	54 Gm. 18 days	W.B.C. 1,800 No granulocytes	Death	Salicylates
Aug. 1937	Bernstein, S. S.: J. Pediat. **11**: 198, 1937.....	6 mo.	♀	N	16 Gm. (orally) also injections 4 wk.	No neutrophils	Death	Not stated
Sept. 1937	McGinty, P.: Unpublished observation.....	19	♀	N	50 Gm. 18 days	W.B.C. 1,350 No granulocytes	Recovery	None
Oct. 1937	Jennings, G. H., and Southwell-Sander, G.: Lancet **2**: 898, 1937	39	♀	W	90 Gm. 21 days	W.B.C. 444 No neutrophils	Recovery	Not stated
Jan. 1938	O'Connell, J. T.: U. S. Nav. M. Bull. **36**: 61, 1938	Youth	♂	W	25 Gm. 7 days	W.B.C. 650 No granulocytes	Death	Probably more sulfanilamide
Jan. 1938	Schwartz, W. F.; Garvin, C. F., and Koletschy, S.: J. A. M. A. **110**: 368, 1938	32	♂	W	56 Gm. 21 days	W.B.C. 800 No neutrophils	Death	Antisyphilitic treatment
Jan. 1938	Berg, S., and Holtzman, M.: J. A. M. A. **110**: 370, 1938	22	♂	W	38 Gm. 16 days	W.B.C. 1,600 No neutrophils	Death	None
Aug. 1937	Mitchell, A. G., and Trachsler, W. H.: J. Pediat. **11**: 183, 1937	Child	..	..	Large doses	Not stated	Death	
Aug. 1937	Model, A.: Brit. M. J. **2**: 295, 1937.....	20	♂	W	54 Gm. 18 days	W.B.C. 600 No neutrophils	Death	

21. Blew, C. L.: A Report of Three Cases of Agranulocytosis, U. S. Nav. M. Bull. **35**: 484 (Sept.) 1937.

22. Klumpp, T. G.: Agranulocytosis Associated with the Administration of Novaldin, a Derivative of Aminopyrine, J. A. M. A. **108**: 637 (Feb. 20) 1937.

23. Benjamin, J. E., and Biederman, J. B.: Agranulocytic Leukopenia Induced by a Drug Related to Aminopyrine, J. A. M. A. **107**: 495 (Aug. 15) 1936.

One recovered, but the other died after the leukocyte count had fallen to 2,700 per cubic millimeter with a total absence of granulocytes.

It should be emphasized that sulfanilamide also produces a severe type of acute hemolytic anemia in many patients, the red cells occasionally being hemolyzed to the extent of from one-half to one million cells a day. Also, in some patients sulfanilamide produces a marked stimulation of the leukocytes, which may or may not be preceded by a moderate depression. I have observed six such patients being treated for various infectious states; the leukocyte counts reached alarmingly high figures during convalescence from the disease (74,000, 56,000, 40,000 and 25,000, with a marked granulocytic shift to the left). This indicates that sulfanilamide produces in some patients a depression and in others a stimulation of leukopoietic activity.

TABLE 2.—*Drugs Reported to Have Caused Agranulocytosis* *

	No. of Cases
Aminopyrine	Over 300
Dinitrophenol	7
Arsphenamine †	20
Antipyrine	2
Derivative of aminopyrine (novaldin)	2
Acetanilid ?	2
Acetophenetidin (phenacetin)?	3
Cinchophen (atophan)?	1
Antimony compound (neostibosan)?	8
Sulfanilamide	11
Quinine ?	4
Gold salts ? ‡	19 (Plum)

* The drugs known to be capable of producing the disease are not followed by a question mark; for the others, followed by a question mark, the evidence is not adequate.

† Hematologic depression limited to granulocytes only.

‡ Hematologic depression not limited to granulocytes.

OTHER DRUGS SUSPECTED OF CAUSING AGRANULOCYTOSIS

In addition to the drugs discussed, which are unquestionably capable of producing the disease, certain other preparations have been suspected by various writers. These include antipyrine, which is the chemical precursor of and closely related to aminopyrine. Groen and Gelderman [24] have reported two cases in which agranulocytosis followed its use. Acetanilid as a causative factor has been suspected by Watkins [25] and Hudnutt,[26] and I have observed a classic attack following the prolonged administration of a patent remedy known as "Dr. Mile's Nervine," the essential ingredient of which is stated to be acetanilid. Acetophenetidin (phenacetin) has been named as the probable causative factor in two instances by Kracke and Parker [2] and in one by Costen.[27]

Shapiro and Lehman [28] have reported agranulocytosis in one patient who was being treated with cinchophen (atophan). Quinine has been suspected as being causative in at least four instances. Zia and Forkner [29] treated a large number of patients for kala-azar with a proprietary preparation of pentavalent antimony compound (neostibosan), and agranulocytosis developed in eight. Plum [3] has reviewed the literature concerning the danger of gold salts and collected nineteen cases in which agranulocytosis apparently followed the administration of this class of drugs. All the preparations that are known to be capable of producing agranulocytosis and those suspected of producing it in rare instances are listed in table 2.

ALLYL-ISOPROPYL-ACETYL-CARBAMIDE (SEDORMID)

Sedormid is a preparation that has become widely advocated for the relief of pain. Although it has not been reported as a cause of agranulocytosis, it has been reported as the causative factor in eleven cases of thrombocytopenic purpura [30] and is included here as another preparation capable of depressing the thrombocytic elements of the marrow with little effect on the leukocytes. This preparation has been termed nonacceptable for inclusion in New and Nonofficial Remedies and should be used with caution.

THE INCIDENCE OF AGRANULOCYTOSIS

In an effort to determine whether or not agranulocytosis is becoming less frequent in the United States, I have procured data from the United States Bureau of Vital Statistics relative to the deaths reported from it within the years 1934, 1935 and 1936. The figures for those years as well as for 1931, 1932 and 1933 are shown in table 3.

It will be noted that there has been very little change in the yearly number of deaths reported during the past six years. However, death reports are not a reliable index to the incidence of the disease. It can reasonably be assumed that in the past three years recognition and diagnosis of the condition has become far more frequent than in preceding years. However, it could be claimed that the number of cases is larger now and that more patients recover because of better methods of treatment. It has been my experience that the condition is now rarely seen in the southeastern part of the United States.

A study of the report of the Bureau of Vital Statistics shows a decreased incidence of the disease in prac-

TABLE 3.—*Deaths from Agranulocytosis in the United States*

1931	417
1932	453
1933	444
1934	503
1935	380
1936	407

TABLE 4.—*Deaths from Agranulocytosis in the Larger States*

State	1934	1935	1936
California	42	33	17
Illinois	39	17	22
Massachusetts	32	8	5
Michigan	13	9	13
Minnesota	13	9	8
Missouri	17	8	9
New Jersey	28	19	14
New York	65	51	36
Pennsylvania	42	35	34

24. Groen, J., and Gelderman, C. J.: Agranulocytose (Maligne Neutropenie) door Due Geneesmiddelen, Nederl. tijdschr. v. geneesk. **78:** 3444 (July 29) 1934.

25. Watkins, C. H.: The Possible Role of Barbiturates and Amidopyrine in the Causation of the Leukopenic State, Proc. Staff Meet., Mayo Clin. **8:** 713 (Nov. 22) 1933.

26. Hudnutt, O. D.: Case of Agranulocytosis with Recovery Following Administration of Concentrated Liver Extract, J. Michigan M. Soc. **34:** 440 (July) 1935.

27. Costen, J. B.: Agranulocytosis: Appearance of the Early Pharyngeal Lesion: Three Cases, One Apparent Recovery, Ann. Otol., Rhin. & Laryng. **42:** 372 (June) 1933.

28. Shapiro, Shepard, and Lehman, Lester: A Case of Agranulocytosis Following Ingestion of Cinchophen, Am. J. M. Sc. **192:** 705 (Nov.) 1936.

29. Zia, L. S., and Forkner, C. E.: The Syndrome of Acute Agranulocytosis and Its Occurrence as a Complication of Kala-Azar, Am. J. M. Sc. **188:** 624 (Nov.) 1934.

30. Hoffman, A. M.; Kahn, Julius, and Fitzgibbon, J. P.: Thrombocytopenic Purpura Following Allyl-isopropyl-acetyl-carbamide (Sedormid), J. A. M. A. **110:** 725 (March 5) 1938.

tically all the larger states, as shown in table 4. In this connection I have solicited the opinions of several hematologists in different geographic areas of the country. There seems to be general agreement that the disease is not observed as frequently now as during recent years; this opinion is shared by Custer and Fitzhugh of Philadelphia, Heck and Watkins of Rochester, Minn., Parker of Boston, Sturgis of Ann Arbor, Mich., Haden of Cleveland and Cannon of Chicago.[31] Madison stated that the disease has increased recently around Milwaukee, with some attacks apparently caused by sulfanilamide.

Such statistics as are available from the larger medical centers show a high peak in the incidence during the years 1933 and 1934, with a decrease up to this time, although no institution has had a sufficient number to make figures of any considerable value. Sturgis states that agranulocytosis did not commonly exist before 1922 and then had an increasing incidence, which reached its peak about three or four years ago, followed by a decline in frequency; this is affirmed by observations in large clinics in which all patients have routine blood examinations.

In view of such fragmentary evidence it seems logical to assume that agranulocytosis is decreasing in incidence, in particular that which follows the administration of aminopyrine. However, in the future this decrease may be counterbalanced by an increasing number of attacks following the administration of sulfanilamide. In view of Plum's report from Denmark, in which it is clearly shown that the incidence of the disease in that country closely paralleled the consumption of aminopyrine, there can be little doubt that the decrease in this country has been dependent on the amount of aminopyrine consumed.

Even if it is possible for all physicians to cease using aminopyrine the disease will not disappear as long as the public is able to purchase this drug over the counter in drug stores. There is much evidence to indicate that the administration of aminopyrine is being curtailed by some physicians. However, in the last case of agranulocytosis that I observed the disease followed the prolonged administration of amytal compound, yet the physician in charge assured me that he had not used aminopyrine in the treatment of this patient because he was cognizant of the dangers of that drug. Apparently he did not know that amytal compound is a mixture of aminopyrine and a barbituric acid preparation. This illustrates the deplorable tendency to prescribe drugs without knowing what they contain and indicates the extent to which pharmacology is dominated by pharmaceutical manufacturers. Aminopyrine is still included with many other preparations in compounds that have been given a variety of names, few of which indicate the presence of the drug. A list of such preparations is shown in table 5. This is an incomplete list and does not include patented remedies for the relief of pain, whose virtues are so loudly extolled over the radio and through other advertising mediums. No doubt agranulocytosis will continue to follow the administration of aminopyrine from three sources: first, from the occasional physician who prescribes it; second, from physicians who unknowingly use it when it is incorporated with other pharmaceutic agents, and, third, from the purchase of proprietary and patented remedies from drug stores by the patients themselves.

31. Personal communications to the author, June 1938.

In an effort to control the incidence of agranulocytosis the physician should refrain from the use of aminopyrine or analgesic agents that contain it; second, he should warn his patients against the dangers of self medication, particularly the purchase and use of pain-relieving remedies for which the formula is not available; third, the physician who is using agents such as sulfanilamide in the treatment of severe infectious states or is using arsphenamine and other organic arsenicals should watch the patient carefully for signs of possible hematologic depression by frequent studies of the blood; fourth, the physician should take an active part in the program of public instruction relative to the dangers

TABLE 5.—*Preparations That Should Be Used with Caution Because They May Depress the Leukocytes*

Preparations Containing Aminopyrine	
Allonal	Dymen
Alphebin	Dysco
Amarbital	Eu Med
Amidol	Gardan
Amido-Neonal	Gynalgos
Amidonine	Hexin
Amidophen	Ipral-Amidopyrine
Amidopyrine (aminopyrine)	Kalms
Amidos	Lumodrin
Amidotal compound	Midol
Amifeine	Mylin
Aminol	Neonal compound
Am-Phen-Al	Neurodyne
Ampydin	Nod
Amytal compound	Optalidon
Analgia	Peralga
Antabs	Phenamidal
Baramid	Phen-Amidol
Barb-Amid	Phenopyrine
Benzedo compound	Pyramidon
Cibalgine	Pyraminal
Cinchopyrine	Sequit
Compral	Yeast-Vite
Cronal	

Drugs Known to Produce Depression of the Marrow	
Dinitrophenol	Antipyrine
Arsphenamine	Sulfanilamide
Novaldin	Sedormid (thrombocytopenia)

of these preparations, for only if he does so can the public become informed as to these dangers. Certainly it will not get this information from drug stores and pharmaceutical manufacturers.

CONCLUSIONS

1. The cause of most agranulocytosis is now definitely established.

2. The disease has practically disappeared from Denmark because aminopyrine is no longer used in that country.

3. Approximately 80 per cent of drug-produced agranulocytosis is caused by the administration of aminopyrine or one of its compounds, with a lesser percentage being caused by the administration of dinitrophenol, arsphenamine, sulfanilamide, and novaldin.

4. The disease is decreasing in incidence in the United States, probably because of the more cautious use of aminopyrine by the medical profession.

5. The number of cases of agranulocytosis from the use of sulfanilamide will probably increase in the future, particularly if this drug is incorporated in patented remedies and indiscriminately sold to the public under noninforming names.

6. Physicians should attempt to prevent this disease by caution in the use of these drugs, by instruction of patients concerning their purchase in drug stores and by programs of public instruction.

THE PRESENT STATUS OF THE SERUM THERAPY OF LOBAR PNEUMONIA

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It is not often that the Section on Practice of Medicine requests a report on the present status of the treatment with a well known remedy of a common acute illness. Generally the best remedy soon becomes the most popular, and all physicians quickly learn which one that is. Such, however, has not been the case in the treatment of pneumonia. Apparently the recent interest in the serum treatment of lobar pneumonia has expressed itself in so many forms, other than in curing patients, that one may well ask questions about merit and popularity.

It takes a bold person to judge merit and popularity in a problem that vexes most of the medical profession in an issue that is changing with great rapidity. It is impossible to say very much in finality now. However, after a number of years of personal experience with the serum treatment of pneumonia and after a very thorough search of the current literature, I find that enough information is at hand to warrant a consideration of the present status.

A good many years of my experience have been with slow methods of pneumococcus typing and with treatment using unrefined serum of low potency. But in the past three years, i. e., from October 1935 to April 1938, my associates and I at the Cincinnati General Hospital have studied slightly more than 1,000 cases, in 230 of which potent serum was used. The fatality rate in the serum treated group was 8.2 per cent.[1] The expected fatality in this hospital and under the same circumstances of medical care as judged by 318 cases (not treated) of the same types was 34 per cent. This is a reduction of 76 per cent in fatality rate. We have treated type I and type II pneumonia mainly and these only in the early stages, i. e., before the end of the fourth day of sickness. For type I and type II pneumonia this reduction in fatality rate at the Cincinnati General Hospital just about describes the merits of serum treatment wherever it has been used consistently in early cases that are accurately typed for specificity.

Similar merit has been reported from (what should be called) the pneumonia centers in New York and Boston hospitals. In two states that have pioneered in the use of serum in the home as well as in the hospital the results are not very different. This merit of serum treatment for type I and type II pneumonia is described in all the standard textbooks of medicine of recent date and in up-to-date works on treatment. The superiority of serum treatment over all other cures should no longer be doubted.

In addition to the reports from two Eastern hospitals which have been most quoted, I find eighteen separate reports (all with adequate controls) from Ohio, Michigan, Connecticut, Pennsylvania, Canada, England, Scotland and Denmark, all attesting a 50 to 60 per cent reduction (ours is 76 per cent) in mortality rate for type I pneumonia and from 40 to 50 per cent reduction for type II pneumonia.

There is, however, considerable variation in the actual and final figures, so that if the worst results with serum in one place are compared with the best results without serum at another place, no great merit is seen in serum treatment. Such a method of estimating merit is entirely fallacious, for adequate controls are possible and have been published. I could find no report of completely unsatisfactory results from serum, save only of certain experimental serums that are not recommended for general use. It is true that serum treatment in its present form (i. e., with rapid accurate typing and potent refined serum) has been evaluated in but a few localities; but where it has been tried it is found to be good. Whether one can say good enough for all localities depends mainly on the types found in each locality. To arrive at this estimate of merit I have searched 184 current journal articles, mostly from January 1937 to the present, all recommending the use of serum.

USE OF PNEUMOCOCCUS SERUM

How popular is this treatment; i. e., how extensive has been the use of antipneumococcus serum? To judge from reports in current literature only a few individuals and a few hospitals have actually made general use of it. A questionnaire of hospitals conducted by the American Medical Association[2] showed that very few large municipal hospitals (where the patient ill with pneumonia is most likely to go) were typing the pneumococci in their cases of pneumonia. Questions were asked of 4,565 hospitals (2,595 hospitals replied, and only 1,850 hospitals reported being equipped to type).

A survey of my own[3] on the distribution of serum for the first eleven months of 1937 shows that from an estimated number of 160,413 cases, serum was provided for 34,185 cases of type I and type II pneumonia combined. This estimate of the number of cases treated is based on the information that 3,418,500,000 units of serum was sold. Using 100,000 units as an average for one patient, we find that 34,185 patients with type I and type II pneumonia (or 21 per cent of the estimated total number of cases of these types) received serum treatment in the first eleven months of 1937. This estimate of the annual number of cases of type I and type II pneumonia, i. e. treatable types, was furnished by Dr. McGill of the United States Public Health Service in a report in 1937.

Considering the complete want of any other specific for pneumonia, there is still a considerable gap between merit and popularity (only 21 per cent treated). It is in contemplation of that gap between merit and popularity that many of the facts are to be found that are important in making progress toward pneumonia control. To me it is apparent that, wherever specific serum is being used, accurate bacteriologic diagnoses are being made and accurate vital statistics are being accumulated. By contemplating the present status of serum therapy, much may be learned about pneumonia control. If all the obstacles in the way of early diagnosis and exact bacteriologic diagnosis (typing) were understood and overcome, the progress of pneumonia control would be much more rapid.

In May 1938 THE JOURNAL published the special report of the Pneumonia Advisory Committee of the

Read before the Section on Practice of Medicine at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 15, 1938.

1. Ruegsegger, J. M.: Pneumonia: A Three Year Survey, in preparation.

2. Pneumonia Mortality and Pneumococcus Typing Facilities, editorial, J. A. M. A. **109**: 1910 (Dec. 4) 1937.

3. Data on the distribution of serum for 1937 were supplied through the courtesy of Dr. W. T. Harrison of the U. S. Public Health Service, the National Drug Company, E. R. Squibb & Sons, Lederle Laboratories, Inc., Eli Lilly & Co. and Gilliland Laboratories.

U. S. Public Health Service to the Surgeon General.[4] It was not a lengthy report, but it contained forty-nine specific recommendations in the way of studies to be made, facts to be found, experiments to be done—mainly bacteriologic—and a few social experiments as well. All these recommendations are based on the new knowledge of pneumonia that may come from the wide use of complete typing.

SUITABILITY OF SERUMS FOR GENERAL USE

Are the present serums suitable for wide and popular use? The answer is yes, if the type incidence is the same all over the country and if typing facilities are available. The actual facts in the matter of type distribution are meager, and but few cities have done the work necessary to learn what the true type incidence may be. New York, Massachusetts, Connecticut, Pennsylvania, three cities in the Middle West (Detroit, Cincinnati and Minneapolis), one on the Pacific Coast (San Francisco) and three in the South have published significant observations on type incidence. Eight large cities of the Eastern and Northern United States show from 43 to 66 per cent for the combined treatable types, I and II. But it has been generally said that upward of 50 per cent of cases are due to pneumococci of types I and II; but, so far as the literature concerned shows, 50 per cent is too high. Meanwhile other serums have been added, thus increasing greatly the so-called treatable types. Especially in the South does this rule of 50 per cent fail. Reports from four large Southern cities show that cases of type I and type II pneumonia combined range from 19 per cent to 35 per cent. Sometimes there is a considerable fluctuation as may result from a change in the plan of typing. I find that when typing is done only to search for pneumonia of types I and II, in order to ascertain whether or not serum treatment is indicated, the results may be quite different from those in laboratories charged with complete typing regardless of the hope to treat. In the one instance the laboratory is satisfied to report whether or not the physician has type I or type II pneumonia to treat, whereas with complete typing the laboratory must tell what type actually is present. This additional responsibility on the laboratory has made for thoroughness, which may greatly revise the ideas about type incidence. For instance, in one city of the South the incidence of type I and type II pneumonia combined had apparently changed from 5 per cent to 50 per cent in two years.

Another prerequisite to popular use of serum therapy is accurate typing. There has been but little use of serum reported without typing even where bivalent serum of pneumococcus type I and pneumococcus type II combined is employed. How accurate then is typing? In good hands the rapid, direct method of Neufeld seems to be very accurate. In a recent book of great merit, the late Dr. Benjamin White[5] concluded that by this method "there should be few cultures that cannot be classified in the thirty-two fixed types." The Neufeld method applies equally to sputum, but broth cultures and mouse inoculations are frequently needed to check sputum analysis and occasionally to analyze sputum where the direct method fails. The Neufeld method, although simple and easy to learn, requires practice and patience.

4. Special Report of Pneumonia Advisory Committee to Surgeon General, U. S. Public Health Service, J. A. M. A. **110:** 1701 (May 14) 1938.

5. White, Benjamin: The Biology of Pneumococcus, New York, Commonwealth Fund, 1938.

Dr. James Ruegsegger, pneumonia fellow in the Cincinnati General Hospital, has trained a large group of typers for the Ohio State Department of Health as well as every one of the numerous assistant residents who came to our medical service. He finds that these students can master the technic in a week's intense work and relies on these residents for a considerable amount of emergency typing. When sputum is not obtained promptly, we use cultures made from throat swabs and find, as do others, that although slower than direct sputum typing it is a satisfactory method. Blood cultures are found very useful for routine serum therapy and in some circumstances are absolutely essential for accurate knowledge needed for treatment. Blood cultures check the accuracy of sputum typing, especially in cases in which multiple infections may occur. Blood cultures are of aid in calculating dosage, and most writers recommend that a double dose of serum be given to patients who have bacteremia.

CARRIERS

What about the carrier state and the difficult task of deciding whether a mouth organism is important or unimportant? That problem is solved by the combined experience of the bedside doctor and the typer. The gross appearance of the sputum, the scarcity of other organisms and the method of sputum collection or of throat swabbing must all be added to intelligent bedside guessing in a manner rarely practiced in any other clinical laboratory consultation. Prompt and accurate typing is absolutely essential to successful serum treatment and requires an intimate working relation between laboratory and bedside doctor that is rarely to be found, save only where some pneumonia enthusiast has worked for several years. This teamwork must be rehearsed in advance of the onset of the disease. Want of this consultation service spells failure unless the clinician does all his own typing, which is seldom possible. Laboratory delay or confusion can wreck any so-called pneumonia program.

EFFECTIVENESS OF SERUM

Is specific serum administered when accurate typing has been done generally successful? For type I pneumonia, when given early and in large doses, the answer is yes. It is so uniformly successful that if the patient does not improve one should suspect a mistake in typing or the presence of a complication, usually empyema. For type II pneumonia, even with large doses results are not so favorable, but mortality is reduced from an expected rate of 40 per cent to about 20 per cent if treatment is instituted early in the course of the disease. The effectiveness of serums for pneumonia of types V, VII and VIII seems midway between that for types I and II as reported from six separate hospitals during 1937. In our own series for 1937-1938 (which is the time we have had such serum) the result was as good as in type I pneumonia.

In all reports for all serums, the necessity of early treatment is clear. It also appears that the practice of early treatment with serum will eventually effect a definite change in the habits of doctors caring for patients with pneumonia. In diagnosis, the emphasis now will fall on history, symptoms and faint physical signs. Most of the technic of diagnosis, including x-ray as ordinarily taught and practiced, is inadequate for early diagnosis and to recognize complications.

SAFETY

Is serum safely and easily given? Since serum for adults must be given intravenously in large doses as early as possible, certain dangers must be offset by precautions. The Massachusetts Department of Public Health found four deaths among 1,313 treated patients in which the death could be ascribed to the serum. About one fourth of the patients of this series were treated in homes in Massachusetts. In our series there has been one such death among 230 treated patients. In our particular instance, obvious warnings were not seen and understood by the intern giving the serum. We practice as a routine the methods of testing for sensitivity which are accepted everywhere and recommended by Lord and Heffron [6] as well as by Bullowa [7] in textbooks on the serum treatment of pneumonia. We have abandoned the methods of desensitizing; but we do, in doubtful cases, give a test dose intravenously and watch the blood pressure for a drop that might presage a dangerous shock.

As to other types of serum, i. e. other numbers, especially rabbit serum, I am not so sure, but I think that in the hands of skilful physicians most patients can be treated safely with any form of serum. I have searched thoroughly most of the state journal literature up to and including May 1938 and I do not find any account of serum accidents or any warnings against the present methods now advanced, except that the State Department of Health [8] in New York did issue a warning in THE JOURNAL about the general use of rabbit serum.

I find a trend to shorten the intervals between doses and to raise the dose, especially for type II pneumonia. We now treat many of our patients with but two doses, one of 20,000 units and an hour later one of 60,000 or 80,000 units of type I. For type II pneumonia we generally give 20,000 then 60,000, 60,000 and 60,000 at hourly intervals.

In all cases in which blood cultures are positive we administer, as does every one, twice the usual dosage. This supplementary dose is usually given on the following day, as blood cultures require from twelve to twenty-four hours for incubation. We do not assign to an expert the giving of serum. All our interns and residents give it as a part of the hospital routine. Sensitive or doubtfully sensitive patients are treated by interns but under immediate supervision of the fellow in pneumonia. In passing I may describe our hospital as a city hospital without a special pneumonia service and without many of the facilities that university hospitals enjoy. The cost of the serum is borne by public funds, but the laboratory is maintained and the director provided by private funds.

COMPLICATIONS

What about serum therapy and complications? Early successful serum treatment prevents and cures pneumococcic septicemia and in this manner reduces the incidence of suppurating complications. If such suppuration has already started before serum treatment has been completed, horse serum is probably of no value. This want of value in pneumococcic suppuration may not be true of rabbit serum. Even with large doses, a considerable percentage of serum failures is found to be due to undiscovered empyema. All writers with experience emphasize the importance of searching out early empyema. We have learned that serum is of no value in endocarditis, and we were unsuccessful in treating pneumococcic meningitis.

6. Lord, F. T., and Heffron, Roderick: Pneumonia and Serum Therapy, Revised Edition, New York, Commonwealth Fund, 1938.
7. Bullowa, J. G. M.: The Management of the Pneumonias, New York, Oxford University Press, 1937.
8. Warning Against Premature Use of Rabbit Serum for Pneumonia, New York, J. A. M. A. **110**: 747 (March 5) 1938.

SUMMARY

Complete typing of all cases, through the entire thirty-two types, is the keystone of serum treatment and may provide the necessary information leading to the prevention of pneumonia.

In parts of the United States where typing has been practiced, treatable types comprise more than 50 per cent of all cases of pneumonia, save only in certain districts of the South. Now that other therapeutic serums (V, VII, VIII and probably many more by the device of rabbit serum) have been developed, a much higher percentage will be treatable.

Neufeld typing of the sputum and cultures of various body fluids is a rapid and accurate method of bacteriologic diagnosis of pneumococcus types.

The selection of patients for efficient and satisfactory treatment requires early diagnosis by the physician and intimate consultation with the bacteriologist. Serum must be given in adequate dosage by vein, and a double dose must be given when blood cultures are positive. Serum must be injected slowly after sensitivity tests are found negative, but the entire dose should be given during the first twenty-four hours. Serum accidents have been extremely uncommon and the danger of reactions early and delayed should rarely preclude treatment.

Refined and concentrated horse serum for type I and type II pneumonia is a well established and satisfactory remedy. When given during the first twenty-four hours it is a specific comparable to the best specific biologic remedy, save only diphtheria antitoxin. When given within the first four days of the disease, the mortality rate of pneumonia may generally be reduced more than 50 per cent. In our experience of three years the mortality was reduced 76 per cent.

Until 1937 the use of serum treatment, as judged from published results, was restricted to a few places—Massachusetts, New York, Maine, Connecticut, Ohio and Michigan. In 1937 approximately 20 per cent of patients with type I and type II pneumonia in the United States were treated with serum.

Cincinnati General Hospital.

ABSTRACT OF DISCUSSION

DR. EDWARD S. ROGERS, Albany, N. Y.: In regard to the arbitrary selection of a period of four days from the onset of the disease as being the crucial interval for serum treatment, our experience in New York State has added a little further information. In the specific treatment of 2,027 type I cases, we have found that we can extend that period of usefulness to include the fifth day, the case fatality rate for cases treated on that day being, roughly, 16 per cent. One must be cautious in attempting to predict the incidence of pneumonia and particularly of individual types in the anticipated experience of any particular community. I am not sure how Dr. McGill, whom Dr. Blankenhorn quotes, derived his figures, but the basis on which such calculations usually are made is rather questionable. Dr. Blankenhorn has suggested such caution and also the futility of assuming that the type incidence once established for any given area will necessarily remain the same for that area. Dr. McLaughlin of Pittsburgh has told me that in his experience in the past three years he has encountered a change in the incidence of type II pneumococcus pneumonia from about 5 per cent to

about 35 per cent. In New York State we have observed massive shifts in the prevalence of type specific penumonia in a number of areas during the past few years. The use of repeated sputum specimens is unquestionably worth emphasis. A patient treated early and adequately with specific serum who does not respond to that treatment within a period of from twelve to eighteen hours may well be subjected to a complete bacteriologic reexamination. Under such circumstances another type of pneumococcus often may be found. In this respect the proper use of blood cultures will also prove of great value. Time does not permit a discussion of the problem of sensitivity to horse serum, though I imagine it might interest this group particularly. I would like to say, however, that we are finding the significance of the skin test and the ophthalmic test rather difficult to understand in relation to reactions subsequently encountered. In our type I experience, however, fatalities in any way related to serum administration, whether anaphylactic or more vague in nature, were encountered in less than 0.5 per cent of all cases. There were no deaths from chill or thermal reactions in the entire series.

DR. FRANCIS G. BLAKE, New Haven, Conn.: One of the most frequent questions encountered is What shall be the size of the initial dose? I noticed that Dr. Angevine included 50,000 units within the range of a large dose. I would consider 50,000 units a quite small initial dose, as we rarely use less than 100,000 units. The second important question is How late in the disease is it worth while beginning the use of antipneumococcus serum? I should like to ask Dr. Blankenhorn his opinion on that. The third important question that often arises is How long shall serum therapy be continued in a patient who has not shown clinical response after 200,000 or 300,000 units? It would be interesting to know Dr. Blankenhorn's opinion from his own experience.

DR. JAMES L. DUBROW, Des Moines, Iowa: It is important to know, when dealing with a case of pneumonia, how the diagnosis is made. Emphasis was laid on the bacteriologic examination of the sputum. However, some patients may be carriers, or the sputum may be scanty. In my opinion a chest roentgenogram shows important early signs in suspected cases of pneumonia. In some cases of early pneumonia physical examination may disclose a rale or two and one may think the chest is normal, yet the stereogram shows a patch of haziness which is a possible sign of beginning pneumonia. For corroboration in doubtful cases the chest roentgenogram should be repeated some hours or a day later, when an opacity may be shown occupying one or two lobes. Furthermore, the history of the case should be taken into consideration. Highly significant is the onset of the illness. Some claim that in lobar pneumonia atelectasis is demonstrated on the roentgenogram. The question of atelectasis is closely bound up with that of bronchostenosis. If the patient has not had a sudden acute illness, one may be dealing with a bronchogenic tumor. It may not be a case of pneumonia at all. Early blood cultures should be made, especially when the sputum is scanty or the sputum typing gives contradictory results. In such cases it is well to do a lung puncture, remove a little serum and have it examined bacteriologically for pneumococci. Once one has decided that one has a case of pneumococcic pneumonia and knows the type causing it, the question of serum therapy arises. It is well to take into consideration the leukocyte response, temperature rise and how ill the patient looks. Before administering serum it is important to determine by history, skin and conjunctival tests whether the patient is allergic. I have had cases of type I pneumonia in which the patients (some allergic) got along nicely without serum.

DR. M. A. BLANKENHORN, Cincinnati: I am indebted to Dr. Rogers for pointing out that the fourth day is not critical and that one should include the fifth day. Selection of patients was determined by economic reasons rather than epidemiologic ones. It was not possible to afford the serum for everybody, so the early cases, in which the most good could be done, were treated and the fourth day was arbitrarily chosen. Dr. Rogers emphasized the importance of typing. There seems to be a hope in wishful thinking that we won't need to type because eventually a single serum or chemical will do for all types. Certainly the trend now is for type specific serum and the "typing" of patients for treatment absolutely essential. Dr. Blake asked a pertinent question with regard to the size of the initial dose. This dose is 20,000 units. I regard that as a testing dose. Then in one hour after the first dose I give the second dose, which may be 60,000 units or even 80,000 units, so the entire 100,000 is given within two hours. I expect to get the entire dosage in the vein within a few hours, unless the blood culture is found to be positive, in which case the repeated dose, which is equal to the first dose, is given within twenty-four hours. "How late to start treatment?" I have no opinion on that. Late treatment was not given because we couldn't afford it and because the importance of coming into the hospital early has been emphasized. "How long to continue treatment after 200,000 or 300,000 units has been given?" I have not set a time. I rarely give serum after the second day, unless blood cultures are positive. I generally stop on 300,000 units, and I have had so few failures that the question of going on with more serum rarely arises. When it does, complications are looked for. Early cases, of course, are being treated. Dr. Dubrow answered his own question when he asked about the diagnosis and then immediately mentioned the history. I think that for early recognition of the disease the history is more important than physical signs. The roentgenogram is of importance only in confirmation. The patients in our medical service are examined repeatedly and we think the most important physical sign for early diagnosis is the crepitant rale. The history and sputum are of a great deal more importance.

APNEA OF THE NEWBORN AND ASSOCIATED CEREBRAL INJURY

A CLINICAL AND STATISTICAL STUDY

FREDERIC SCHREIBER, M.D.

DETROIT

It is with some temerity that a neurologic surgeon undertakes to address an obstetric section on the subject of cerebral injury in the newborn. The two specialties have a common responsibility, however, to the child showing clinical evidence of such injury, and if either can contribute anything to reduce the number of these tragedies a critical analysis of the subject is certainly desirable.

The evidence obtained during this study indicates that cerebral asphyxia at birth may cause permanent degenerative changes in the brain with clinical neurologic manifestations. The correlation between recent neuropathologic, pharmacologic, physiologic and obstetric observations may be traced. From experience and research it is found that most cases of cerebral birth injury are associated with apnea at birth.

The significance of the association may be clarified by means of a schematic diagram showing the relationship between the stages of oxygen deficiency and results of that deficiency and the possible degrees of cerebral damage from a deficient oxygen supply. The causes and effects of various degrees of fetal anoxemia are represented in figure 1. The circle represents a wheel the segments of which turn only to the left. The hub of the wheel is the respiratory center in the

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Owing to lack of space, this article has been abbreviated for publication in THE JOURNAL. The complete article will appear in the author's reprints.

Read before the Section on Obstetrics and Gynecology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 15, 1938.

Constructive criticism and encouragement were given by many of my colleagues, in particular Drs. George Kamperman, Nathaniel Gates, Joseph B. De Lee, Norman Miller, Ward Seeley, Lewis Daniels, Owen Foster, Nathan B. Eddy, Louise Eisenhardt, Gabriel Steiner, Frank Murphy, David Levy, Edgar Ma tmer, W. C. C. Cole, W. L. Brosius and the research departments of Parke Davis & Co. and Eli Lilly & Co.

medulla. This center, first described by Legallois in 1812, depends for its proper function on the interchange of oxygen and carbon dioxide. The factors that are known to depress the respiratory center are oxygen want, drugs, gases and organic change. The obstetric counterparts of these depressing agents are normal birth trauma, abnormal birth conditions, operative intervention, oxytocics, analgesic drugs and anesthetic gases. The arrows pointing to the respiratory center indicate the degree of depressing effect on the center by these agents in relation to the clinical effect on the newborn.

The quadrants designated as phases I, II, III and IV relate the changing situations in the fetal cerebral oxidation processes. Phases III and IV, especially, concern the neurologist, since these phases include the clinical manifestations of disturbed cerebral function. The line between phases III and IV has been designated as the vital line. This line indicates the division between

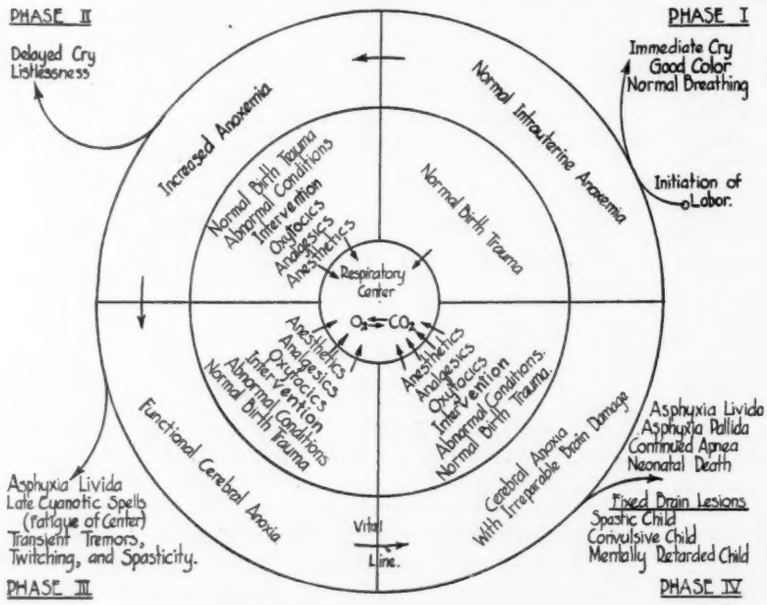

Fig. 1.—Schematic representation of the correlation between the incidence and extent of apnea and the occurrence of cerebral symptoms.

transient neurologic manifestations and irreparable damage to the brain in the newborn.

The "wheel" is set in motion by the initiation of labor. The extent of its rotation before birth varies in every case, depending on the occurrence of such unpredictable factors as the incidence of natural birth difficulties; the weight, second stage metabolism, and blood oxygen capacity of the mother, and, in addition, her individual susceptibility to the drugs and anesthetics employed to abolish pain.[1] The temperature existing in the mother and in her environment during labor and delivery must be considered. A further flip of the wheel by a depressing dose of an analgesic drug may spell the difference between a normal and a permanently damaged baby if the vital line is crossed. It appears to me that the effect of chance, in some of the cases studied in which anesthetics and analgesic drugs have been employed in labor, has been allowed to participate to such an extent as to be somewhat disturbing to the professional conscience.

Since apnea is a clinical indication of anoxemia, it must be regarded as dangerous to the newborn infant if anoxemia is shown to be dangerous in itself. The most vital and rapid effect of anoxemia is on the brain, where isolated groups of cells may quickly die if there is an oxygen want (anoxia) in the tissues. Such localized cell death is irreparable and can be seen microscopically if the baby perishes. However, these localized areas of necrosis resulting from cerebral anoxia do not necessarily cause the death of the fetus or infant. In case of survival the clinical evidences of localized necrotic lesions or their resultant intracerebral scars and atrophy are neurologic disturbances whose pattern depends on the location and extent of the damaged areas.

Since the analgesic drugs employed during labor are a frequent cause of dangerous apnea in the newborn, it seems that, if brain damage is later found in cases in which considerable analgesia has been used, this injury can properly be ascribed, either wholly or in part, to the optional drugs that have been given to the mother in labor.

During a ten year period (Jan. 1, 1928-Dec. 31, 1937) 685 patients were seen in whom a relationship was suspected between the manner of birth and the later neurologic manifestations of damage to the brain. Most of these patients were seen at the Children's Hospital of Michigan, Detroit, and the remainder were seen in consultation. Of the 685 children, 131 were seen because of convulsions, sixty-nine because of spasticity, 130 for mental retardation, 248 because of combinations of these symptoms and the remaining 107 for miscellaneous neurologic conditions.

Cases subject to suspicion of postnatal infection or trauma were excluded from the group, as were those in which congenital or familial factors might have significance in cerebral symptomatology: associated meningocele, harelip, familial feeblemindedness, erythroblastosis, hemorrhagic disease and congenital heart disease. Finally, the group was limited to those infants born in one county during the ten year period. These restrictions left 500 cases in the study group.

Study of the records for the group immediately showed that 155 of the babies were born under conditions over which a physician has little or no control: precipitate, breech, twin or premature deliveries. For some cases all the birth data were obtainable—the obstetric difficulties and the oxytocics, analgesia and anesthesia used. In others, although it is known that the mothers were given "shots" and "pills" the amounts are not known. When not available from the birth records, information on the condition of the infant at birth was given by a parent when the child was brought in because of neurologic manifestations. Only histories of apnea were accepted in which the baby was reported as remaining "black" or "blue" for a considerable period after delivery, there were recurring "blue spells," or the infant did not breathe and had to be resuscitated.

The occurrence of apnea in the group of 155 infants born under uncontrollable circumstances (precipitate, breech, twin and premature delivery) is recorded in table 1 in relation to the type of delivery used.

In table 2 the occurrence of apnea is related to the various adjuvants used during the process of childbirth.

1. Schreiber, Frederic, and Gates, Nathaniel: Cerebral Injury in the Newborn Due to Anoxia at Birth, J. Michigan State M. Soc. **37**: 145 (Feb.) 1938.

The remaining 345 subjects of the 500 were all full term infants; in this group there were no precipitate, breech or twin deliveries. Table 3 presents the relationship between the type of delivery and the occurrence of apnea for all the 345 whose condition at birth was known. Of the 345 infants in this group, 180 were known to have been born in the hospital and 135 were known to have been born at home; for thirty the birthplace was not recorded.

The incidence of apnea within this group in relation to various forms of adjuvant treatment during childbirth is tabulated (table 4).

In table 5 the data from tables 2 and 4 on the occurrence of apnea are summarized and given in the percentage of those cases about which information was available. The incidence of apnea in the group composed of precipitate, breech, twin and premature deliveries is greater than in the full term group.

From table 5 it can be seen that the majority of cases in this group (500) showing evidence of cerebral damage presented one factor in common—apnea at birth. The term apnea is used in its broadest sense and includes all cases in which there was delayed respiration, asphyxia livida or asphyxia pallida was evident or resuscitation was required. Of the 500 cases analyzed in the tables it may be seen that apnea in some degree was present in approximately 70 per cent of the cases in which the condition at birth was known. Fourteen mothers are known to have received nitrous oxide, 211 received ether and forty-eight received nitrous oxide-ether anesthesia. In the forty-five cases of these two groups (total group of 500) in which

TABLE 1.—*Type of Delivery Related to Apnea in Those of the 345 Cases of Full Term Pregnancies for Which the Data Were Available in Which the Child Later Showed Cerebral Symptoms*

Type of Delivery	Condition at Birth			Apnea at Birth	Late Apnea: Condition at Birth		Birth and Late Apnea	Total Apnea
	Known	Good	Unknown		Known	Unknown		
Spontaneous	140	68	27	53	8	1	19	81
Forceps	105	33	18	56	10	2	16	84
Cesarean	2	..	1	..	..	..	2	2
Version-extraction	18	2	2	10	..	..	6	16
Unknown	13	1	27	7	..	3	5	15

TABLE 2.—*Relationship Between the Occurrence of Apnea in the Group of 155 Cases of Precipitate, Breech, Twin and Premature Deliveries in Which, After Delivery, Symptoms of Cerebral Damage Were Seen: Analgesia and/or Anesthesia—and Induction—Used During Childbirth*

	Condition at Birth			Apnea at Birth	Late Apnea: Condition at Birth		Birth and Late Apnea	Total Apnea	Incidence of Apnea, per Cent
	Known	Good	Unknown		Known	Unknown			
No anesthesia or analgesics	23	10	2	8	2	..	5	15	65.2
Analgesics only	2	2	1	..	1	..	..	1	50.0
Anesthesia only	18	12	..	5	3	..	1	9	50.0
Anesthesia and analgesics	29	9	2	13	2	1	7	23	6.7
Anesthesia known, analgesics unknown	9	3	..	5	..	..	1	6	
Anesthesia unknown, analgesics unknown	25	4	31	17	..	5	4	26	
Anesthesia known, shots and pills	9	2	..	4	..	..	3	7	
Anesthesia unknown, shots and pills	4	1	..	2	..	..	1	3	
Medical induction	10	3	1	3	2	1	4	10	90.9
Surgical induction	7	5	..	1	1	..	1	3	42 9
Oxytocics	10	6	1	3	2	..	1	6	60.0

TABLE 3.—*Type of Delivery Related to Apnea in the Group of 155 Cases in Which the Data Were Available*

Type of Delivery	Condition at Birth			Apnea at Birth	Late Apnea: Condition at Birth		Birth and Late Apnea	Total Apnea
	Known	Good	Unknown		Known	Unknown		
Spontaneous	180	34	22	37	6	3	9	55
Forceps	11	3	7	5	1	1	3	10
Cesarean	2	..	..	2	..	..	..	2
Version-extraction	20	5	2	8	1	..	7	16
Unknown	6	..	7	3	..	2	3	8

TABLE 4.—*Relationship Between the Occurrence of Apnea in 345 Full Term Infants Who, After Delivery, Showed Symptoms of Cerebral Damage; Analgesia and/or Anesthesia—and Induction—Used During Childbirth*

	Condition at Birth			Apnea at Birth	Late Apnea: Condition at Birth		Birth and Late Apnea	Total Apnea	Incidence of Apnea, per Cent
	Known	Good	Unknown		Known	Unknown			
No anesthesia or analgesics	7	5	..	2	..	..	..	2	28.6
Anesthesia only	57	31	5	18	3	1	8	30	51.7
Anesthesia and analgesics	86	40	2	33	10	1	13	57	65.5
Anesthesia unknown, analgesics known	1	..	..	1	..	..	..	1	
Anesthesia known, analgesics unknown	23	7	4	11	1	..	5	17	
Anesthesia unknown, analgesics unknown	56	10	60	36	2	4	10	52	
Anesthesia known, shots and pills known	34	10	..	16	2	..	8	26	
Anesthesia unknown, shots and pills known	10	2	..	6	..	..	2	8	
Medical induction	28	13	2	10	3	..	5	18	64.3
Surgical induction	7	2	..	2	1	..	3	6	85.7
Oxytocics	46	22	4	16	6	2	8	32	66.7

no analgesia or anesthesia was used, 38 per cent showed evidence of apnea at birth or within the first few days. It must be remembered that all these patients are abnormal, with cerebral symptoms. The incidence of apnea in all the full term babies, born spontaneously, without drugs or anesthesia, during 1936 at Herman Kiefer Hospital, Detroit, was 5.76 per cent, approximately one seventh of the occurrence in the neurologically abnormal group.

Apnea indicates the presence of some degree of anoxemia with its attendant cerebral anoxia, but serious

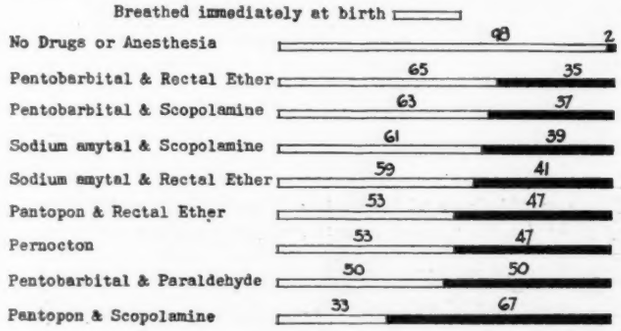

Fig. 2.—Barbiturates and hypnotics in labor; effect on initial respirations of infants.

anoxemia may be present without clinical evidence of apnea. It would seem that apnea is undesirable from the clinical standpoint since it appears in such a high percentage of cases that later show evidence of damage to the brain. Apnea is commonly found in a higher percentage of cases when analgesia and anesthesia are employed in labor than when no analgesia or anesthesia is used.[2] This fact is graphically illustrated in figure 2, adapted from the work of Irving, Berman and Nelson.[3] These authors state that, "all methods [of analgesia] used delayed the initial respiration of the infants to some extent, since a control series of cases in which delivery was effected without any anesthetic showed only 1.9 per cent of infants who did not breathe immediately at birth." [4]

Regardless of the associated conditions in the cases of suspected cerebral birth injury under consideration, the majority were recruited from those infants who did not breathe immediately at birth—a group comparable to those represented by the blacked-in areas in figure 2.

One of the toxic effects of all drugs used to produce analgesia in labor is depression of the respiratory center.[5] Snyder and Rosenfeld, working with animals, have shown the depressing effect of analgesic drugs administered to the mother on intra-uterine respiratory movements. Such cessation of respiratory movements may be taken as an index of anoxemia, since, according to Haldane and Priestley,[6] "no existing physical or chemical method of discriminating differences in reaction approaches in delicacy the physiological response to the breathing." It may be assumed that intrauterine asphyxia may take place under similar circumstances in the human fetus. A large initial dose of an analgesic drug may depress the respiratory center of the mother to such a degree that a dangerous anoxemia ensues in the fetus, with resultant anoxic changes in the brain. However, the interval between the administration of the drug and the birth of the fetus may be of sufficient duration to allow the respiratory center of the fetus to reestablish itself, even though cerebral damage has already resulted, and the anoxemia that existed in utero is therefore not evident when the infant is born.[7] Although permanent degenerative cerebral change may have taken place in such cases, the respiratory center itself was probably spared and normal breathing was observed at birth. Anoxemia, however, makes the respiratory center susceptible to fatigue,[6] and this may be the explanation for the frequent occurrence of late apnea in these cases.

I have applied the term "asphyxia occulta" to the particular group of cases which came with evidence of damage to the brain and in which, during labor, a dose of analgesic drug had been given beyond the ordinary pharmacologic dosage, although the infant's record of birth showed no signs of apnea. This group of patients includes many of the apparent inconsistencies in the correlations between the administration of analgesics and anesthetics and the occurrence of apnea. Apnea of the mother necessarily results in anoxemia of the fetus. Anesthetists generally agree that the cyanosis shown by mothers under the influence of analgesic drugs improves when they come to the birthroom and receive oxygen with anesthesia. Fetal brain tissue, being more sensitive to narcotization, probably is the first to suffer anoxic changes if the drug-induced respiratory depression is severe enough.[8] Some mothers have shown permanent cerebral change following analgesic delivery when the child also showed evidence of cerebral damage. In other cases the child apparently showed no evidence of cerebral damage, although the mother showed neurologic symptoms following analgesic delivery.[1]

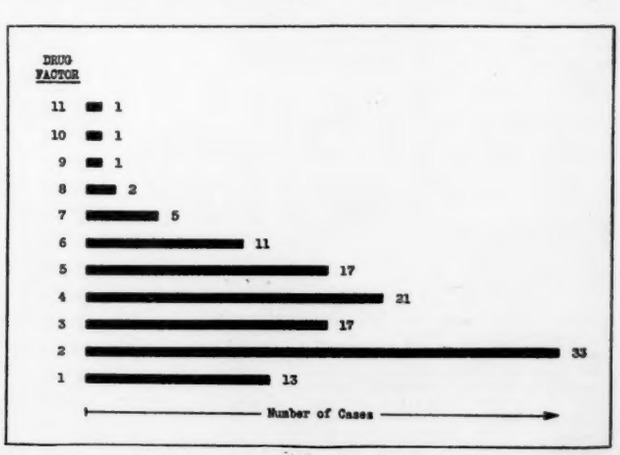

Fig. 3.—Maximum drug factor of analgesics administered in any eight hour period during childbirth to mothers of 122 babies who later showed evidence of cerebral damage.

2. Eastman, N. J.: Fetal Blood Studies: V. The Role of Anesthesia in the Production of Asphyxia Neonatorum, Am. J. Obst. & Gynec. **31:** 563 (April) 1936.

3. Irving, F. C.; Berman, Saul, and Nelson, H. B.: Barbiturates and Other Hypnotics in Labor, Surg., Gynec. & Obst. **58:** 1 (Jan.) 1934.

4. In a series of 1,523 births, which included all the infants born alive in one hospital during the year 1936, a total of 139 infants, born spontaneously without any analgesia or anesthesia, are comparable to the series of Irving and his associates.[3] Eight, or 5.8 per cent, of the infants in this group were cyanotic.

5. Rosenfeld, Morris, and Snyder, Franklin: Effect of Anesthetics on Fetal Respiration, J. Pharmacol. & Exper. Therap. **57:** 139 (June) 1936. Eastman, N. J.: Panel Discussion on Cyanosis in the Newborn, J. Pediat. **9:** 262 (Aug.) 1936. Snyder, Franklin, and Rosenfeld, Morris: Direct Observation of Intra-Uterine Respiratory Movements of the Fetus and the Role of Carbon Dioxide and Oxygen in Their Regulation, Am. J. Physiol. **119:** 153 (May) 1937.

6. Haldane, J. S., and Priestley, J. G.: Respiration, New Haven, Conn., Yale University Press, 1935, p. 97.

7. Clifford, S. H., and Irving, F. C.: Analgesia, Anesthesia and the Newborn Infant, Surg., Gynec. & Obst. **65:** 23 (July) 1937.

8. Jung, P. (of Göttingen): Der Uebergang von Arzneitmitteln von der Mutter auf den Fetus, Therap. Monatsh. **28:** 104 (Feb.) 1914.

No attempt has been made to determine the exact role of dystocia, operative intervention, intracranial hemorrhage and the use of oxytocics, anesthetics or analgesics and whether these are responsible for cerebral damage at birth.[9] I wish merely to emphasize the fact that apnea, from whatever cause, may be dangerous to the fetal brain. Cerebral anoxia has been found to cause intracranial hemorrhage even though trauma is not a factor.[10] Drugs that inhibit labor are also a causative factor in the present increased need for intervention.[11] Thus, analgesics and anesthetics, which are optional therapeutic auxiliaries, are probably the cause, in some cases, of intracranial hemorrhage—and certainly of increased surgical intervention.

Various drugs and combinations of drugs were used to obtain birth analgesia in this series of cases. In 122 deliveries for which the exact drugs, doses and times of administration are known, the distribution was as follows: morphine alone seven, morphine and barbiturates seven, morphine, scopolamine and barbiturates eleven, barbiturates alone nineteen, scopolamine and barbiturates nineteen, scopolamine alone twenty-eight and morphine and scopolamine thirty-one.

TABLE 5.—*Incidence of Apnea in the Two Groups of Cases in Which Data Concerning Apnea Were Available, Tabulated in Percentage, and the Composite of the Two Groups*

	345 Full Term Deliveries	155 Precipitate, Breech, Twin, and Premature Deliveries	500 Composite Group
Apnea at birth.....	61.7	63.9	62.3
Late apnea.....	8.6	11.2	9.4
Apnea at birth and later.	16.8	18.5	17.3
Total apnea.....	68.9	72.0	69.9

When barbiturates were used in combination with scopolamine, the dosage that was usually followed was the one that has been described by Irving, Berman and Nelson:[3]

> The initial dose of sodium amytal by mouth was from 9 to 12 grains, depending upon the weight of the patient. This drug was repeated three to four hours later in from 3 to 6 grain doses if indicated. Forty-five minutes after the initial dose of sodium amytal one one-hundredth or one one-hundred and fiftieth of scopolamine was given subcutaneously and was repeated later as soon as the patient began to complain of pain.
>
> The initial dose [pentobarbital and scopolamine] is from 4½ to 6 grains by mouth which may be increased if desired, and it is repeated according to the same indications as govern the use of sodium amytal.

If scopolamine alone was used, the dosage advocated by Daniels and Tamblyn,[12] based on their experience in 453 cases, was usually followed:

> One 1/100 of a grain (of scopolamine) is given every half hour for 3 doses and then one 1/100 grain every two hours. . . . The average dose of scopolamine was 5 1/100 grain. The smallest dosage given which resulted in complete amnesia was 2 1/100 grain and the largest dose used in this series was 21 1/100 grain.

Such obstetric dosages[13] are difficult to reconcile with the ordinary clinical doses as defined by the pharmacologist.[14] The ordinary hypnotic dose of sodium amytal is from 3 to 9 grains (0.2 to 0.6 Gm.) at intervals of not less than six hours. The hypnotic dose of pentobarbital is given as from 1½ to 3 grains (0.1 to 0.2 Gm.), with severe intoxication from doses over 7½ grains (0.5 Gm.).[15] Severe toxic effects with respiratory depression from 3 grains of pentobarbital have been reported.[16]

Of scopolamine, Sollmann[15] states in his 1937 manual: "There are great individual variations in the response to scopolamine and therefore in its toxicity. *The variable toxicity is due mainly to idiosyncrasy, for it occurs in the purest samples.*" He further says: "Small doses (1/300 to 1/75 grain) have produced serious poisoning with cardiac and respiratory collapse.

Fig. 4.—Generalized cerebral atrophy in an idiot with asphyxia pallida at birth.

. . . *With ordinary individuals it is not safe to exceed 1/120 grain,* repeating this smaller dose every six to eight hours if necessary."

The ordinary clinical adult pharmacologic dose of the drugs known to have been employed in this series of cases in which cerebral damage was encountered has been assigned a factor value of 1 for purposes of comparison with other cases in which combinations of drugs were used. If the dose used was greater than the ordinary clinical dose, the factor was increased by the proper multiple (or fraction).

9. Data on this subject were accumulated during the study but must await further analysis before publication.
10. Yant, W. P.; Chornyak, John; Schrenk, H. H.; Patty, F. A., and Sayers, R. R.: Pub. Health Bull. 211, Studies in Asphyxia, U. S. Treasury Department, August 1934.
11. Young, James: Maternal Mortality and Maternal Mortality Rates, Am. J. Obst. & Gynec. **31**: 198 (Feb.) 1936.
12. Daniels, L. E., and Tamblyn, E. J.: Scopolamine Alone for the Relief of Pain During Labor, J. Michigan State M. Soc. **32**: 553 (Oct.) 1933.
13. Literature published by the firms manufacturing drugs usually advocates much smaller doses than are used by many practitioners. However, these firms do not hesitate to quote the dosages published in obstetric papers.
14. Cushney, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 11, Philadelphia, Lea & Febiger, 1936. Gutman, Jacob: Modern Drug Encyclopedia and Therapeutic Guide, New York, Paul B. Hoeber, Inc., 1934. Sollmann.[15]
15. Sollmann, Torald: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1937, pp. 373-374, 737.
16. Willcox, William: The Uses and Dangers of Hypnotic Drugs Other Than Alkaloids, Brit. M. J. **1**: 415 (March 10) 1934.

If combinations of drugs were used, the combined factors were added. For example, morphine one-fourth grain (0.015 Gm.) (factor 2) and scopolamine 1/120 grain (0.0005 Gm.) (factor 1) would give a combined drug factor of 3 in this case.

The usual doses of various drugs used have been assigned the factor values given in table 6.

Because of the difficulty in properly evaluating the effect of time, since in most cases the warnings of the pharmacologist regarding the repetition of doses within certain time limits were ignored, I was able to compare the cases only on the basis of the maximum amount of analgesics given in any eight hour period. The drug factors for the 122 patients during the eight hours of maximum administration are shown in figure 3.

It must be borne in mind that this discussion on the effects of drug dosage refers to adults who happen to be in labor. The fact that they are in labor does not protect them against the effects of toxic doses. The usual and most alarming effect is respiratory

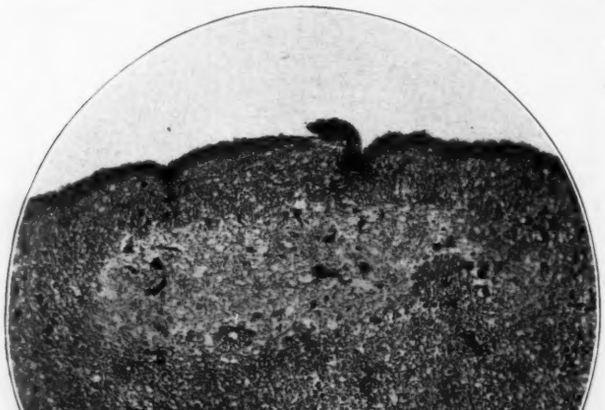

Fig. 7.—Necrosis in section of medulla of an infant cyanotic from birth.

depression. If the mother must contend with drug-induced respiratory depression in addition to the natural exigencies of childbirth, the fetus must also, being dependent on the mother for its oxygen supply until actually born, suffer from the same respiratory depression and at the same time go through the intensely traumatic experience of being born.

GROSS CEREBRAL CHANGES ASSOCIATED WITH ASPHYXIA AT BIRTH

The late microscopic changes of cerebral anoxia are death of neural tissues with gliosis.[10] The gross end result is atrophy of the brain. Such atrophy can often be demonstrated by means of the encephalogram. Pneumographic studies were made on 207 of the infants in this series, of which seventy-three showed generalized atrophy, seventy-five showed localized atrophy, thirty-five showed no demonstrable changes in the roentgenograms and twenty-four of the studies were technically of no diagnostic value. These studies were usually made to determine whether the degree of cerebral atrophy was such that a spastic child could not be expected to respond if orthopedic procedures were attempted. If the cerebral loss was found to be too extensive, the mentally retarded child was regarded as needing institutionalization.

Figure 4 is a reproduction of an encephalogram showing generalized atrophy of cerebral tissue in an idiot born with asphyxia pallida.

MICROSCOPIC CEREBRAL CHANGES IN STILLBORN AND NEONATAL ASPHYXIAL DEATHS

Yant and his co-workers [10] fully described the microscopic changes of anoxic cerebral lesions in animals. These typical microscopic changes of the brain, which Courville [17] later demonstrated in the human being as associated with cerebral anoxia, were found in infants in whom asphyxia has been present for some hours or days. Eisenhardt [1] has pointed out such changes in the brain of a stillborn infant, and more recently Steiner [18] has demonstrated similar "devastation areas" in the brains of newborn infants who perished with evidence of asphyxia (figs. 6 and 7).

Figure 7 shows a section taken from the medulla of an infant who died with convulsions on the third day after birth. There had been numerous apneic spells with cyanosis dating from birth. Dr. Steiner describes the histologic changes:

In the medulla oblongata, involving the dorsal and lateral margin, a circumscribed area is present, the shape of which is oval and the color paler than the surrounding tissue. The size of this area is 0.6 mm. in length and 0.16 mm. in width. The limits of the lesion are sharply defined and quite regular. This area is characterized by a looser meshwork of the glial ground substance, the spaces between the meshes being empty.

A few ganglion cells are seen which show a very definite process of degeneration as evidenced by homogenization and vacuolation of the cytoplasm, pyknosis and decentralization of the nucleus, which is here located in the peripheral part of the ganglion cell. A nerve cell shadow indicating total degeneration of the cell is also present in this area.

The histologic picture is typical for the first stage of a devastation area. The location of this lesion in the medulla oblongata near the nuclei of the tenth nerve may be of particular significance.

TABLE 6.—*Factor Values for Usual Doses of Various Drugs*

	Dose, Grain	Factor
Morphine sulfate	1/8	1
Morphine sulfate	1/4	2
Scopolamine	1/120	1
Pentobarbital sodium (nembutal)	1 1/2	1
Pentobarbital sodium (nembutal)	6	4
Sodium amytal	3	1
Sodium amytal	9	3

SUMMARY

In a series of 500 patients, seen because of cerebral symptoms, approximately 70 per cent of those whose birth record was available had a history of apnea. There was a history of precipitate, breech, twin or premature delivery for 155 of the 500 infants; 345 were full term infants. In those of the group of 155 about whom data were obtainable, approximately 64 per cent had apnea at birth, 11 per cent had late apnea only and 18 per cent had both early and late apnea. The total incidence of apnea in this group was 72 per cent.

In the group of 345 full term infants, the incidence of apnea in the cases presenting a known history was

17. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**: 129 (May) 1936.

18. Gabriel Steiner, research professor of neuropathology, Wayne University College of Medicine, Detroit.

at birth, 62 per cent; late, 9 per cent; early and late, 17 per cent, and total, 69 per cent.

The depressing effect, on the respiratory center, of birth analgesics given in greater than pharmacologic doses bears a direct relationship to the degree of apnea. The extent of the apnea has a direct relationship with the severity of the cerebral symptoms after birth. The severity of the cerebral symptoms is in direct relation to the amount of damage to the brain tissue. From these relationships it appears that analgesics given in greater amounts than the pharmacologic dosage may in many instances be the causative factor of fetal anoxemia, with resultant cerebral damage in the infant.

10 Peterboro Street.

ABSTRACT OF DISCUSSION

DR. C. B. COURVILLE, Los Angeles: My interest in asphyxia has been largely in its pathologic manifestations. This study by Dr. Schreiber would seem to strengthen the conception that the lesions of asphyxia are essentially the same regardless of the mechanism or cause of depression of the respiratory and cardiac centers. Subtotal destruction of the occipital (calcarine) cortex as a result of asphyxia can be demonstrated. This cortical area seems to be particularly sensitive to the reduction in oxygen supply. Laminar degeneration is a slightly less advanced type of lesion. Several laminae of necrosis in the cortex tend to fuse, particularly in the superficial part of the convolution. These foci of necrosis tend to occur about dilated blood vessels, which are obviously larger than those in the apparently normal regional tissues. The presence of these distended vessels in the areas of necrosis suggests that stagnation is one of the factors in producing the ultimate effects of asphyxia. It should be said that asphyxia in the newborn is due to excessive depression of the respiratory and at times the cardiac centers, that necrosis of the cerebral gray matter will occur if spontaneous breathing is absent for any length of time, that this necrosis is not demonstrable histologically unless the infant survives for at least thirty-six to forty-eight hours and that this necrosis is probably responsible for many of the residual symptoms in children that survive. As Dr. Schreiber has emphasized, the respiratory center may be dangerously depressed by anesthetic agents and drugs used in relief of pain during delivery as well as by mechanical means. Excessive depression with such agents is probably less likely to occur in well organized clinics than in deliveries in smaller hospitals or in the home.

DR. J. C. LITZENBERG, Minneapolis: Dr. Schreiber has shown that we are too apt to evaluate our results by immediate considerations only, ignoring more remote consequences. Ever since I observed the extremely high percentage of asphyxiated babies in the Freiburg clinic, where Koenig and Gauss developed "twilight sleep," I have been apprehensive of such extreme cases of apnea. Dr. Schreiber has proved that my apprehensions were justified because the remote consequences are found by the brain surgeon to be serious brain injury. When we do an operation in gynecology, we do not estimate our results by the patient getting off the table alive; we estimate our results by the remote consequences. Have we cured the patient of that for which we operated? In this late furor of painless childbirth, I have no intention of criticizing the relief of pain in labor; but this paper emphasizes that we must evaluate the individual to whom it is safe to give it, the individual to whom it is unsafe to give it, and the remote dangers of apnea following the use of any analgesic. I was impressed when I read the text of this full paper that the majority of all the author's cases in which considerable damage was done had one factor in common; that is, apnea at birth, 72 per cent of them. The 68 per cent who had no analgesia but had apnea also showed the same brain damage. Apnea is evidently a dangerous condition, perhaps more dangerous remotely than immediately. The table which showed the deliveries accomplished without any anesthetic or any analgesia showed only 2 per cent of apnea while with all the different analgesic drugs the cases of apnea ranged from 35 to 67 per cent. Therefore, on the average, when analgesics are used, apnea occurs from seventeen to thirty-three times as often. If the author's thesis is correct, which I believe it is, it behooves us to reevaluate our attitude toward analgesics in labor with the remote as well as immediate results in mind. I feel convinced that he has established his thesis that the degeneration of the cerebral tissue is positively demonstrated and that analgesia beyond the same pharmacologic dose is a causative factor in the fetal anoxemia with the resultant cerebral damage. There are many lessons that can be learned from this paper. The one that has impressed me most is that the question of relieving the pain of labor must be reevaluated, the remote results and not only the apparent immediate results being kept in mind.

DR. CHARLES E. GALLOWAY, Evanston, Ill.: For about five years I have tried my best to look at this problem in a rational manner, because I feel that women in childbirth deserve to have as much of the pain relieved as possible with safety. But I think that physicians must be very careful in the use of analgesics in childbirth, because it is an added factor in fetal mortality. However, whenever one looks at any problem one must look at it as a whole and not from any one standpoint, and I think the pain of childbirth can be safely relieved, at least the intense suffering can be taken from the patient, without damage to the infant. When I heard about this paper I wrote a letter to every man who has taken care of any babies out of Evanston Hospital over the last five years and also to our leading neurologist in the community, who takes care of practically every case of infant mental deficiency. The letter in part was as follows: "In Detroit, and I presume other places in the country, men have been using large doses of scopolamine repeated as many as six times during labor, together with as much as 6 grains of pentobarbital. Consequently, they have had a high fetal mortality. But ever more important, they have found a small percentage of these babies mentally defective or at least constituting what might be called problem children. Those doses of $\frac{1}{100}$ grain of scopolamine repeated time after time is, I think, an abnormal medical procedure, and we at the Evanston Hospital have seldom ever given more than $\frac{1}{150}$ grain of scopolamine at any time, and it has been practically never repeated. We seldom give more than 6 grains of pentobarbital, and only occasionally does it run up to 9 or 10½ grains. Since the five and one-half years we have been using these drugs, they have been administered to only 60 per cent of the patients delivered, and there have been only two maternal deaths among the patients receiving the drugs. Please tell me what you think about the possibility of any mental damage in these babies. I expect to sum up the various answers and incorporate them in my discussion." I received about eleven answers out of thirteen letters, and the consensus among the men who have been treating such cases is that mental damage does not occur. Why the authors get so many cases in one community I cannot see, but I should like to make two statements. One is that such a procedure during labor, of giving repeated large doses of scopolamine, is very poor medical practice. The other is that I think these men have not entirely proved their thesis. I think that more work will have to be done and one will have to compare the incidence of mental damage in cyanotic babies with the incidence of mental damage without cyanosis at birth. Since the world began, about 2 per cent of the population has been born defective mentally and it may even be that a baby is cyanotic at birth because it is mentally deficient. I also believe that one expects a baby with cerebral hemorrhage to be unable to breathe.

Hippocrates' Clinical Records.—The writings of Hippocrates were copied and recopied for centuries, used by Galen, and, more or less garbled, studied almost up to the eighteenth century, when critics began to use them chiefly for historical material. Clinical records of forty-two cases have come down to us from Hippocrates, so clearly treated that Osler and Sydenham took them as model records. Among these cases were quinsy, diphtheria, typhoid fever, pleurisy, dislocations of bones, and injury to the skull.—Hurd-Mead, Kate Campbell: A History of Women in Medicine, Haddam, Conn., the Haddam Press, 1938.

PROCTOLOGIC TUMORS

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AND
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Most modern hospitals have accepted the principle of examining microscopically all tissue removed by operation. While gynecologists adhere to this rule regardless of the size of the specimen, most proctologists regard histologic study as unnecessary when small amounts of tissue are removed, especially when hemorrhoidectomy is performed.

During the last six years we have studied by microscopic methods every specimen removed during anorectal operation, no matter how small the lesion and how harmless its gross appearance. Reviewing our clinical and pathologic records of 951 proctologic patients, it is evident that in the majority of cases nothing has been detected by histologic study which changed the prognosis or treatment based on clinical examination. This, however, is true also in the fields of major surgery and gynecology. There are, on the other hand, so many cases in our material in which the microscopic examination revealed conditions which were not suspected clinically that the routine histologic study of proctologic specimens seems well justified, in the interest of the patient.

Fig. 1.—The intermediate zone of the anal canal is lined with epithelium resembling bladder epithelium. It is a remnant of the fetal cloaca. There were four papillary tumors in this area among our cases.

McCarty,[1] basing his statistics on 150,000 surgical cases, found that routine microscopic examination revealed in 0.5 per cent of all operations a malignant condition which was not suspected by clinical methods or during operation. In our series of 951 proctologic cases this percentage of clinically unrecognized cancer is almost four times higher, namely 1.9 per cent. The conclusion therefore is justified that, more than in other regions, early malignant lesions of the anal canal may closely resemble harmless conditions.

There is considerable confusion in the literature regarding the anatomic limitations of the anal canal. We follow the definition of Rosser,[2] who regards as anal canal the lower portion of the rectum. It coincides with the pars perinealis of the anatomic nomenclature and extends from the perineal flexure of the rectum to the anus. It is narrowed by the sphincters and levators and is the site of anal disease. While the anal canal forms a physiologic and pathologic entity, histologically it is a complex structure. Its interior surface is lined with three different forms of epithelium which are of different fetal origin. The upper zone of the anal canal has typical intestinal epithelium with columnar cells and Lieberkühn glands. The middle or intermediate zone is a remnant of the fetal cloaca and is lined with transitional epithelium as found in the urinary bladder and urethra. This zone extends from the recto-anal line down to the anocutaneous or dentate line. The crypts of Morgagni and the anal ducts are the most important structures of this area. The distal portion of the anal canal is purely ectodermal and is called the cutaneous zone.[3]

Buie [4] limits the term anal canal to only this portion which is lined with squamous epithelium. No glands are found in this zone. Sweat glands of large size, the so-called apocrine glands, sebaceous glands and hair follicles characterize the beginning of true skin or perianal region. The junction between the cutaneous zone of the anal canal and of the perianal region is called anus according to the anatomic nomenclature of Basel. To understand the great variety of anal tumors one has to keep in mind the three different types of epithelium lining the anal canal and its complex fetal development.

The uppermost zone of the anal canal is the favored site of glandular neoplasms. In our series there were fifteen adenomas and thirty-five adenocarcinomas. In the intermediate zone, which is more predisposed to inflammatory lesions than other parts of the anal canal, tumors are relatively rare. We found four benign papillary tumors resembling bladder papilloma, one melanoma and two adenocarcinomas in this area. Distal from the anocutaneous zone there were, in our series, four squamous cell carcinomas, one melanoma and one basal cell carcinoma.

Connective tissue tumors did not show predilection for different portions of the anal canal as did the epithelial growths. There were twelve benign and six malignant tumors. Besides lipomas, fibromas and myomas we found one hemangio-endothelioma, one myxoma, one xanthoma and one myosarcoma, one spindle cell sarcoma and two lymphosarcomas.

Many of the malignant tumors in our material were small and eighteen of the fifty-two malignant tumors were discovered during routine histologic examination of what seemed clinically harmless anal lesions. Two adenocarcinomas and the basal cell carcinoma were completely removed by hemorrhoidectomy and in the specimen removed at the subsequent radical operation after the histologic diagnosis was established no trace of malignant tissue could be detected.

In six of our fifty-two malignant cases, cancer developed in previously existing anal lesions. One adenocarcinoma was found originating in a fistulous tract, one squamous cell carcinoma in a fissure, three adenocarcinomas in hemorrhoid nodules and one basal cell carcinoma in an external hemorrhoid.

In 1931 Rosser [2] reported thirteen cases of anal malignant growths which had some benign pathologic condition as the etiologic agent and further reviewed an

From the Department of Proctology and Pathology, St. Francis Hospital.

Read before the Section on Gastro-Enterology and Proctology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 15, 1938.

1. McCarty, W. C.: The Study of Fresh Tissue as an Aid to Clinical Diagnosis, S. Clin. North America **5**: 701 (June) 1925.

2. Rosser, Curtice: The Etiology of Anal Cancer, Am. J. Surg. **11**: 328 (Feb.) 1931.

3. Tucker, C. C., and Hellwig, C. A.: Histopathology of Anal Crypts, Surg., Gynec. & Obst. **58**: 145 (Feb.) 1934. Tucker, C. C., and Hellwig, C. A.: Anal Ducts, Arch. Surg. **31**: 521 (Oct.) 1935.

4. Buie, L. A.: Practical Proctology, Philadelphia, W. B. Saunders Company, 1937.

additional eighteen cases from the literature which showed some anorectal disease as a forerunner. Of Rosser's thirteen cases, the etiologic factors in seven were fistula, in four hemorrhoids and in two cryptitis and papillitis. Buie and Brust [5] in 1933 reported fifty-one cases of anal malignancy in which thirty-four showed some benign anal lesion as a forerunner. In 1937 T. E. Smith [6] published the results of a review of the literature and personal correspondence with leading proctologists. In his report there are 107 cases of anal

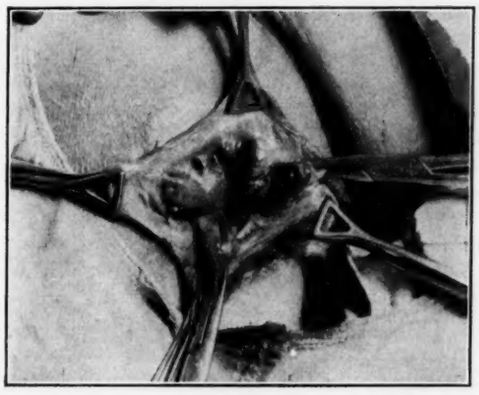

Fig. 2.—The dark tumor at the right appeared clinically as a thrombosed hemorrhoid nodule. Microscopically it was a malignant melanoma.

malignancy developing from benign lesions. He does not include adenomatous polyps, which are generally recognized as precancerous conditions.

Our material of adenomatous polyps could be classified with one exception by histologic criteria as either benign or frankly malignant tumors. Only one polyp showed atypical glands in a small area, probably a transitional stage of a benign into a malignant growth. The fact that hypertrophic anal papillae are often confused with adenomatous polyps has been stressed in a recent paper by Tucker [7] of San Antonio. In several cases the diagnosis of adenoma was made by an occasional proctoscopist, when the location in the dentate line and the whitish surface characterized these structures as enlarged papillae. We agree with Tucker [7] that hypertrophic papillae do not carry a serious prognosis as compared with adenomas.

Not infrequently, patients seek proctologic advice while their symptoms are caused by extra-anal conditions. The complex embryologic changes occurring in the sacral region explain the origin of chordoma (two cases in our material), teratoma (one case) and dermoid cysts. Of pelvic tumors which produced symptoms calling for proctologic examination were one ovarian dermoid which became infected and perforated into the rectum, and one adenomyoma of the rectovaginal septum. A patient with a tumor of the cauda equina consulted first the proctologist on account of anal discomfort. Of interesting tumors in the perianal region we observed a sweat gland adenoma, a myxoma and a hemangioneuromyoma of the glomus type.

REPORT OF CASES

CASE 1.—*History.*—Mrs. H. J., a widow aged 64, admitted to St. Francis Hospital Jan. 15, 1931, had complained of hemorrhoids for the past thirty years. There was no history of bleeding but the patient complained of constipation and constant pain in the back. On examination internal and external hemorrhoids were found. Operation was performed January 16 and tissue was sent to the laboratory.

Pathologic Examination.—There were five nodules of different size, the largest one 1 cm. in diameter, the smallest 4 mm. The surface of the nodules was folded and apparently not ulcerated. No suspicious changes were evident to the unaided eye.

Microscopic examination disclosed that the epithelium of four nodules was of typical appearance, representing either columnar or transitional epithelium. There were slight inflammatory changes in the subepithelial tissue, and large blood-filled spaces were found in the stroma. In one nodule which was taken from the junction between squamous and columnar epithelium there were glands of irregular structure. The lining cells were not well oriented and the nuclei were hyperchromatic. In a few glands several layers of epithelial cells were found. No basement membrane could be made out. These atypical cells had invaded the submucosa and had reached in one place even the muscular layer. Few of the alveoli were filled with mucoid material and exfoliated epithelial cells. No mitotic figures were found. The areas of atypical proliferation were surrounded by round cells.

The pathologic histologic diagnosis was adenocarcinoma at the junction of the squamous and columnar epithelium in one of five hemorrhoid nodules.

The patient was given high voltage roentgen therapy and radium. The radiologist reported that from January 26 to January 31 he administered 600 roentgens, using 15 and 20 cm. portals, a filter of 0.5 mm. of copper and 1 mm. of aluminum, 65 cm. tube distance, from 180 to 200 kilovolts, 8 milliamperes and twenty-five minute treatments. February 2 he administered 50 mg. of radium in a T applicator in the rectum for forty-eight hours. Feb. 18, April 8, Nov. 25, Nov. 28, Dec. 1, Dec. 8 and Dec. 19, 1931, and March 12, 1932, ultraviolet treatment was given. There has been no recurrence to date.

CASE 2.—*History.*—G. W., a white man aged 67, entered the proctologic department of the clinic Sept. 13, 1935, and on rectal examination a fistula in ano was found together with internal and external hemorrhoids and infected anal ducts. The patient complained of pruritus ani.

X-ray examination was negative. The patient stated that he had a chill about once a week. He had a severe chill about three months before, associated with gallbladder colic. X-ray

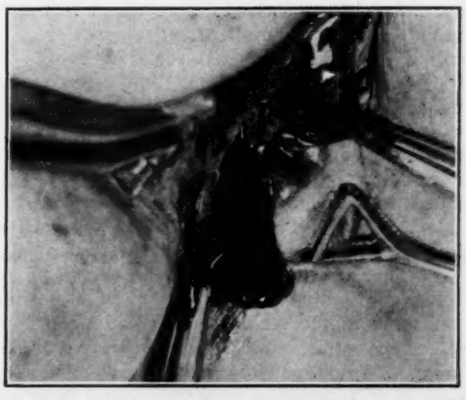

Fig. 3.—Hemangioma of anal canal. Clinical diagnosis, hemorrhoid.

examination showed nonvisualization of the gallbladder and no evidence of stone. The patient had chills and fever as a child when he came to Kansas. A malarial smear gave negative results. On the following day operation was performed at the County Hospital.

Pathologic Examination.—The solid nodule was composed of very atypical glands, which were invading the muscle layer. The epithelium lining the glands showed malignant characteristics. The cells were in several layers and poorly oriented. The nuclei were large and vesicular and had large nucleoli. The stroma was extremely scanty and showed round cell infiltration. In one section a hypertrophied papilla was found

5. Buie, L. A., and Brust, J. C. M.: Malignant Anal Lesions of Epithelial Origin, Journal-Lancet **53**: 565 (Nov. 1) 1933.
6. Smith, T. E.: The Relation of Anorectal Diseases to Malignancy, Proc. Dallas County M. Soc., Sept. 9, 1937.
7. Tucker, V. C.: Comparison of Hypertrophied Anal Papillae and Rectal Polyps, Texas State J. Med. **32**: 810 (April) 1937.

with marked round cell infiltration of the subepithelial tissue. At the proximal base of the papilla, inflammatory changes were found near a duct.

The pathologic diagnosis was adenocarcinoma.

Six weeks later a perineal excision was performed. No evidence of cancer was obtained on microscopic examination.

The patient has remained well to date.

CASE 3.—*History.*—R. C., a white man aged 43, a sales manager, first noticed bleeding from the rectum two years before. The bleeding was small in amount and occurred at irregular intervals. The bowel movements were regular. Pain began about the week previous to admittance to the hospital. Physical examination gave negative results. Proctoscopic examination revealed infected anal ducts, an enlarged papilla at the anorectal line anteriorly which resembled a tumor, and internal and external hemorrhoids. The patient was admitted to St. Francis Hospital Nov. 29, 1937, and operated on the following morning.

Pathologic Examination.—There were eleven specimens varying in size from 2 cm. to 5 mm. Three were covered with skin. Several had large blood vessels.

Microscopic examination revealed several large papillae with markedly hypertrophic epithelium and round cell infiltration. The epithelium showed parakeratosis. There were several ducts with definite inflammatory changes in the wall. The

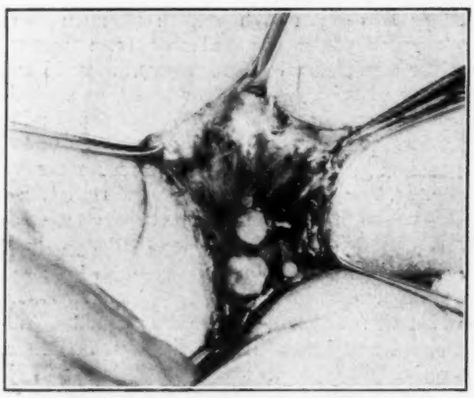

Fig. 4.—Two fibromas and one lipoma in anal canal.

internal and external nodules had large blood vessels with thin walls. No inflammatory changes were found in the skin. In one hair follicle extensive proliferation was noticed. The cells were invading the surrounding tissue and there was formation of small cysts. The structure was that of early basal cell carcinoma.

The pathologic diagnosis was external and internal hemorrhoids and infected anal ducts, hypertrophic papillae and minute basal cell carcinoma.

The patient was given high voltage roentgen therapy and radium. Jan. 5 to Jan. 12, 1938, 3.414 roentgens was administered; 15 by 15 and 20 by 20 cm. portals were used with 1 mm. copper and 1 mm. aluminum filter, 50 and 60 cm. tube distance, 185 kilovolts and 8 milliamperes. January 22, 50 mg. of radium was administered in the rectum in a rectal applicator in two layers of rubber rotated 120 degrees every four hours for twelve hours, 12 by 50, or 600 milligram hours.

The patient will continue to be examined proctoscopically every two months. There has been no recurrence to date.

CASE 4.—*History.*—Mrs. L. J., aged 45, white, American, a housewife, for the past two years had had some pain in the rectum but no bleeding. Four years before she had a hysterectomy for uterine fibroids, which on microscopic examination showed no evidence of malignancy. She was admitted to the hospital in May 1937 for a rectal operation. A diagnosis was made of internal and external hemorrhoids, with a papilloma at the anorectal line. There were several internal hemorrhoids and thrombosis of external hemorrhoids.

Pathologic Examination.—The section showed well preserved surface epithelium consisting of squamous cells with some hornification of the superficial layer. In the subepithelial stroma cross sections of two anal ducts were found. They were lined with transitional epithelium. The lower third of the section consisted of an atypical glandular growth. The tumor consisted of ducts which varied in size and form. There were many solid strands without lumens. The tumor cells were poorly differentiated. They were cuboid and varied in size and staining quality. Some mitotic figures were found. There was no evidence of secretory activity. The stroma between the ducts was extremely scanty. There were no inflammatory changes. The location of the glandular growth and the presence of two typical anal ducts suggested the origin of this adenocarcinoma in the anal ducts.

The pathologic diagnosis was adenocarcinoma of the anal canal originating in anal ducts.

SUMMARY

The clinical and histologic study of 951 proctologic cases emphasizes the wide range of pathologic possibilities causing anal symptoms and the close resemblance between harmless and the most malignant anal lesions. One third of our malignant lesions were discovered by routine histologic examination of clinically benign lesions. Rossers'[2] theory that cancer may develop in long standing benign anal lesions was substantiated by six of our own cases.

A comparison of the clinical and pathologic diagnoses in our 951 cases proves the value of routine microscopic examination in proctologic practice.

ABSTRACT OF DISCUSSION

DR. CURTICE ROSSER, Dallas, Texas: Those who have attended the meetings of this section during the past five years will recognize that this is the third of a series of clinicopathologic papers presented by these authors, a valuable type of report in which the clinical observations of one author are synchronized with the gross and microscopic study of his confrère. In my work in the wards of Baylor University Hospital in Dallas for some years I have noticed this association of benign lesions in the anal canal. In a recent analysis of twenty-five cases of cancer of the anal canal I found that in 87 per cent of them there was an associated benign lesion. There are certain ex cathedra statements which get into the literature more or less casually, which are repeated and copied from one paper or textbook to another, until it would seem that it would require a charge of dynamite to extricate them. Such a statement was that of Paul Kraske, some fifty years ago, that he saw no particular evidence that benign lesions of the anal canal were etiologic agents in cancer. That statement, unsupported by any evidence, has been copied in at least a hundred papers. It crept into the first edition of a standard textbook on tumors, for example, and it has gone through four editions without any change in that textbook. This fact is the reason for presenting evidence that a benign growth in the anal canal may precede and in some way cause the following malignant lesion. As Drs. Tucker and Hellwig have shown, routine biopsy is absolutely essential in the surgery of all presumably benign lesions. Practically one third of their cases of malignancy were discovered in apparently benign lesions, and that, I believe, is sufficient warrant for our insistence on this particular premise.

Dr. L. E. BROWN, Corona, Calif.: That all apparently benign lesions of the rectum and anus should be sectioned and studied under the microscope is shown clearly in two cases which I have had within the past year. Two children, one 18 months and the other 2 years of age, each had a polyp from 1.5 to 2 cm. in diameter. On removal and section, they showed adenocarcinoma grade I. In one of these, to date, the tumor has not returned. In the other one there is another tumor of about the same size that has developed on the opposite side of the rectum. If children 2 years of age or less have adenocarcinoma, certainly it behooves us to consider other tumors in older persons as precancerous tumors, and therefore they should be sectioned and studied.

DR. EDWARD G. MARTIN, Detroit: In discussing this paper, may I add a theory in which I thoroughly believe. One must

differentiate between so-called precipitating causes of cancer and the primary etiologic factor itself. In my opinion, cancer no matter where it is found is caused by an individual susceptibility to an unknown something which as yet remains undefined; something which permits the initiation of the malignant drive. If the use of the term is not too hackneyed, call it protracted allergy. This theory lends itself reasonably to any discussion bearing on the etiology of cancer. Injury is often considered an etiologic factor in cancer of the breast, yet there are probably a thousand injuries in which no cancer develops to each one that does; the individual susceptibility, in other words, is lacking. Consider cancer in any location and the current discussion of its cause; the same reasoning applies. If smoking a pipe caused cancer of the lip or tongue without an individual susceptibility, there would be a thousand times as many cases as there are. If anal disease, such as fistula and hemorrhoids, were an important factor in the etiology of cancer, anal cancer, which is comparatively rare, should be found daily. Such work as has been presented by the authors is of the utmost importance in forming a background for the study of cancer, and without such pioneer work little would be known about cancer. The observations which have been made disclose the desirability of caring for all anal disease and more careful examination leading to such care. Statistics do not prove that cancer is hereditary, and as a matter of fact the incidence of cancer, strangely enough, has been found to be greater in the family histories of those without cancer than it has among those patients who suffer from the disease.

OSTEOMAS OF PARANASAL SINUSES AND THE MASTOID PROCESS

REPORT OF CASES

BERT E. HEMPSTEAD, M.D.

ROCHESTER, MINN.

Osteomas that arise in the paranasal sinuses are not common. Occasionally they are discovered in routine roentgenologic examination of the sinuses. They are not diagnosed clinically or even suspected of being present until either evidence of intracranial complications becomes manifest or external deformities appear. From time to time, articles have appeared that contain reports of cases and give the number of cases previously reported. It is not the purpose of this paper to give a detailed review of the literature; rather, it is to stress methods of handling cases. In 1935 Dr. Carmody reviewed the cases reported up to that time.

ETIOLOGY

The etiology of these bony growths never has been determined. The ethmoid bone is developed from cartilage and the frontal bone is developed from membrane. Osteomas develop frequently at the site of the fronto-ethmoidal suture. Arnold [1] advanced the hypothesis that cartilaginous rests were present and that these enlarge and develop later into bone. He pointed out that where tissues of different embryologic origin come together there is a predisposition to growth of tumors.

Against this hypothesis is the fact that no cartilaginous débris ever has been found in these tumors and that tumors appear at sites where this difference in embryologic derivation does not exist, such as at the recessus nasalis of the frontal bone, at the maxillary antrum and at the tip of the mastoid bone. Virchow believed that the site of origin of such tumors is the diploe of the frontal bone. Scarcely would this explain occurrence of the growth in other places. Infection has been suggested as a possible cause, but many times the tumor is present without any evidence of infection, either macroscopic or microscopic. A history of trauma is obtained many times. The blow, however, usually is so insignificant that probably it is not the etiologic factor. Bornhaupt [1] advanced the hypothesis that such tumors originate from the periosteum.

PATHOLOGY

These tumors may be hard and eburnated in structure, they may be spongy, or they may consist of a mixture of these two types of structure. Growth is very slow. Usually the tumor is attached by a pedicle of cancellous structure. This growth can prevent drainage of the sinus and thus can give rise to a pyocele or mucocele, which may be the direct cause of deformity.

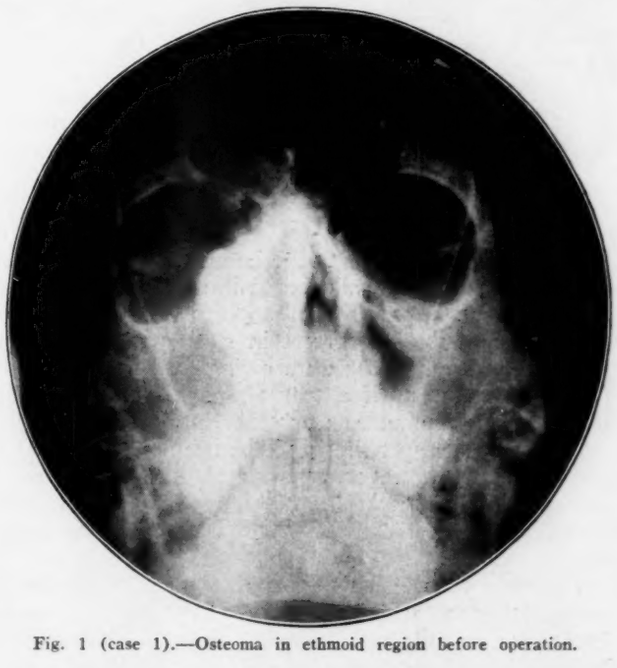

Fig. 1 (case 1).—Osteoma in ethmoid region before operation.

DIAGNOSIS

The small osteoma which elicits no symptoms is discovered only in routine roentgenologic examination of the paranasal sinuses. This type of osteoma should be reexamined subsequently at periodic intervals and, if any evidence of growth appears, should be removed.

The patient who has an osteoma usually presents himself because of pain, external deformity or symptoms due to an intracranial complication. Roentgenologic examination is of the greatest service in indicating the exact site of the tumor and whether or not it has invaded the cranial cavity. This point must be determined carefully by stereoscopic examination, since the surgical approach depends much on this. Presence of pyocele or mucocele cannot be determined always preoperatively because the results of examination of the nose can be negative. If the nasofrontal duct is occluded, conditions are ideal for development of either pyocele or mucocele.

OPERATIVE REMOVAL

Cushing [2] in 1927 reported four cases in which osteoma of the fronto-ethmoidal region occurred, with

From the Section on Otolaryngology and Rhinology, the Mayo Clinic.

Read before the Section on Laryngology, Otology and Rhinology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 15, 1938.

1. Quoted by Armitage, George: Osteoma of the Frontal Sinus, with Particular Reference to Its Intracranial Complications and with the Report of a Case, Brit. J. Surg. **18**: 565-580 (April) 1931.

2. Cushing, Harvey: Experiences with Orbito-Ethmoidal Osteomata Having Intracranial Complications, Surg., Gynec. & Obst. **44**: 721-742 (June) 1927.

intracranial complications. Operation in all was performed by use of an osteoplastic flap which allowed exposure of the tumor from above. In each instance the osteoma had pushed the dura ahead of it and it was not possible to separate the dura from the tumor without producing a tear. Two of these patients died of meningitis. The other two patients were benefited by use of a fascial stamp taken from fascia lata and placed over the tear in the dura. This prevented occurrence of cerebrospinal rhinorrhea with subsequent meningitis. Cushing called attention to the fact that removal of such osteomas is a serious operation and that the ophthalmologist, the neurosurgeon and the rhinologist should consult and decide on the best method of approach. He said that there could be no more permanence to the boundaries of a surgical specialty than there could be to the boundaries of the Balkan states.

Fig. 2 (case 1).—Osteoma removed from ethmoid.

He is undoubtedly correct in stating that if a tear is likely to occur in the dura owing to separation of it from the tumor or if a tear already is evidenced by presence of pneumatocele or other intracranial complication, surgical approach should be from above. Harris [3] and Carmody,[4] however, reported cases of a like tumor associated with cerebral extension of the lesion; the tumor was removed successfully by use of the usual incision for the fronto-ethmoidal type of operation.

Presence of infection in the frontal or ethmoidal sinus makes the approach used by Cushing much more hazardous, as meningitis or infection and subsequent loss of the bone flap may occur. In view of the fact that most often an associated sinusitis is present, it seems to me that the usual fronto-ethmoidal approach will not only permit removal of the tumor but also assist adequate handling of the infection. If, in the course of operation, it becomes evident that there is danger of tearing the dura, operation can be stopped after thorough drainage has been established and after the sinusitis has been cared for; the tumor can be removed at some future time by the method used by Cushing.

Most osteomas are not associated with extension of the lesion to the cerebrum and can be removed through the fronto-ethmoidal incision.

CONCLUSIONS

1. Osteomas of the paranasal sinuses are not common.

2. Most osteomas can be removed through the fronto-ethmoidal incision.

3. If osteomas do not involve the dura or cribriform plate, removal by the method of Cushing is illogical.

4. Pyocele or mucocele of the sinuses can be handled best through the fronto-ethmoidal incision.

5. Osteomas associated with intracranial complications are cared for best through the transfrontal approach.

6. If osteomas are associated with intracranial complications and with definite infection of the sinuses, operation might be done in two stages with advantage.

REPORT OF CASES

CASE 1.—A youth aged 17 years came to the clinic Jan. 7, 1935, complaining of bulging of the left eye, epiphora and pain in the orbit. Bulging had been noticed for three weeks, pain for about three months and epiphora for five months. There had been no intranasal symptoms. His general health had been good. Vision and visual fields of both eyes were normal. The left eye protruded downward and outward.

Roentgenologic examination gave evidence of the presence of a large tumor, apparently of bone, that filled the left ethmoidal region and protruded into the left orbit (fig. 1). The bony mass also could be palpated with a probe in the left middle meatus.

January 12, operation was performed under intratracheal anesthesia. The incision was made in the left brow and was extended down the side of the nose. The periosteum was retracted and the tumor was found presenting at the region of the inner canthus. The tumor was of such density that it could not be removed in pieces. The os planum and parts of the lacrimal, nasal and superior maxillary bones were removed. The osteoma was then grasped with a rongeur, was rocked from its bed and was delivered entire. The growth measured 4.5 by 4 by 2.5 cm. (fig. 2). The wound was closed. Convalescence was uneventful. The patient was dismissed on January 26, at which time the wound was healed. The diplopia, which had developed postoperatively, had disappeared and the eye was in its normal position, the exophthalmos having disappeared (fig. 3).

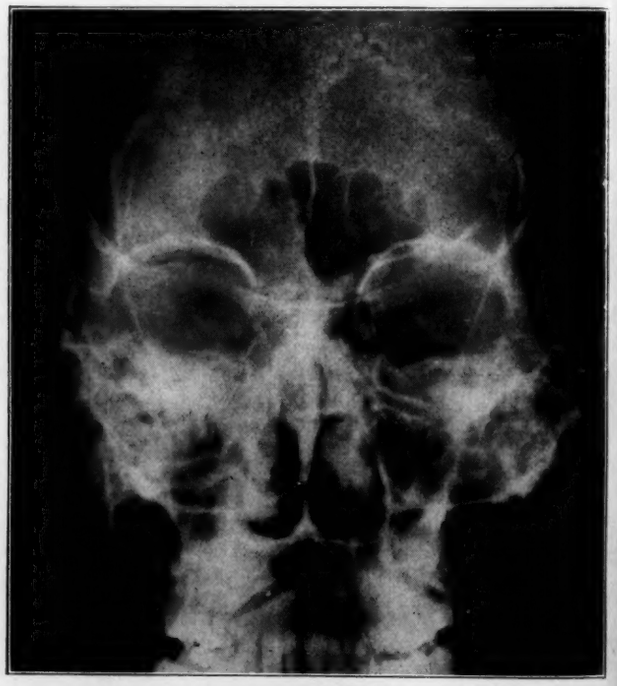

Fig. 3 (case 1).—Appearance after removal of osteoma from ethmoidal region.

In case 2 a large osteoma was situated on the mastoid process. This is the only case ever seen at the clinic and I can find no similar case reported in the literature in English. Several cases, however, have been reported in the German literature.

CASE 2.—A woman aged 22 consulted us at the clinic on Feb. 27, 1928, because of pain behind the left ear. She gave

3. Harris, Robin: Osteoma of the Frontal Sinus: Report of Two Cases, Laryngoscope **38**: 331-346 (May) 1928.

4. Carmody, T. E.: Osteoma of the Nasal Accessory Sinuses, Ann. Otol., Rhin. & Laryn. **44**: 626-643 (Sept.) 1935.

the history of discharge from this ear six years previously; the discharge ceased in a few days. The discharge did not recur but, four months before she came to the clinic, she had noticed a mass behind the left ear and some pain. Examination gave evidence of a normal membrana tympani and normal hearing. There was a hard, firm mass, about 2 cm. in diameter,

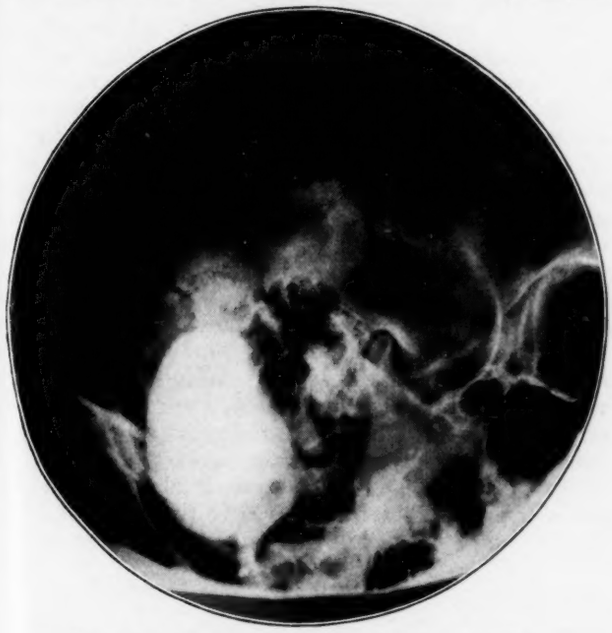

Fig. 4 (case 2).—Osteoma of mastoid before operation.

lying over the tip of the mastoid prominence. Roentgenologic examination gave evidence that this was an osteoma. Surgical removal was not advised (fig. 4).

The patient returned to the clinic May 6, 1929, and stated that she had experienced no trouble with the ear since her last visit. She again returned Jan. 7, 1935, because of abdominal pain. She was referred to the Section on Otolaryngology and it was noted that the tumor was enlarged markedly. Roentgenologic examination gave evidence that the mastoid cells were not involved. The patient was desirous of having this tumor removed because of its size.

Under general anesthesia the growth was removed and it was found attached to the tip of the mastoid. This attachment was cut through with a chisel and the growth, measuring 6.5 by 5 by 3.5 cm., was removed (fig. 5). The bone along the attachment was removed in order to prevent recurrence. The wound healed by primary union.

The pain complained of by this patient was not caused by the osteoma but by an unerupted wisdom tooth. This was removed.

ABSTRACT OF DISCUSSION

DR. GEORGE H. WILLCUTT, San Rafael, Calif.: The subject of osteoma of the paranasal sinuses is of interest because many of us who are not associated with the larger clinics and hospitals don't see many of these cases. In 1935 in Toronto Dr. Carmody reported a number of cases of osteoma of the frontal sinus and also included some of the antrum. Dr. Carmody had attacked those also by the direct method rather than by the upper or more complicated method of Dr. Cushing. Osteomas arising in this region are not common. In the last decade more cases have been reported, possibly because of more careful diagnosis. A differential diagnosis is sometimes difficult unless microscopic examination of the tissue removed is done. Most writers seem to agree that the etiology of these growths is debatable. Dr. Hempstead outlined well the various theories and hypotheses of Arnold and Bornhaupt and Virchow and others. The technic of Dr. Harvey Cushing, which he presented in 1927, was to attack these cases from above, making a big osteoplastic flap. He stressed the dangers and the seriousness of such a procedure and it rather discouraged the average operator from attacking the condition. Dr. Hempstead advances the idea that a much more simple method is feasible. The osteoma isn't the bugbear that it appeared to be from Dr. Cushing's point of view. Naturally, if one should run into a case of extension into the cranial cavity, it might be more difficult to attack it by this method, but one could do the first step of the operation and then at a later date go in from above, or one could get somebody else to go in from above who was more familiar with that technic. It is a revelation to find that this tumor can be attacked by the average man without the necessity of becoming an intracranial surgeon. Dr. Hempstead's mastoid osteoma case is extremely interesting. I was unable to find any reference to a similar case in American or English literature.

DR. THOMAS E. CARMODY, Denver: I don't know anything about osteomas of the mastoid because I have never seen one, nor did I see anything in the literature about it. Osteomas, like other conditions, may come all at once. Of the four that I reported of the frontal sinus (I also reported two of the maxillary sinus at that time), two came within two weeks and the other two came within two years (all of them came within two years), so one might run across many of them in a short time or one may not see any for several years. I had seen only one before in twenty-five years of practice. Dr. Hempstead's idea of the technic of the operation is the same as mine. I do not think it necessary to make a great operation of this, even though the cranial cavity has been invaded. In two of my cases the cranial cavity had been invaded. In one it gave no symptoms. In the other it gave marked symptoms, because the patient had an aphasia and paralysis of the arm and leg on the right side. This cleared up after operation but the man had an epileptic attack. There is a possibility in opening through the nasofrontal duct, because it was also involved with the orbit and the ethmoid, that the entrance of air and water was possible. There is a possibility that there was some pressure on the brain or on the dura in this case. Another patient had epilepsy before the tumor was removed. There was only a slight opening in the posterior wall of the sinus in this case, and the epilepsy was not relieved by removal of the tumor. Since my report, I have found twenty-two cases in the literature —fourteen frontals, two ethmoids, five maxillaries, and one involving the maxillary and frontal sinuses. There are a great many of these cases seen that have not been reported.

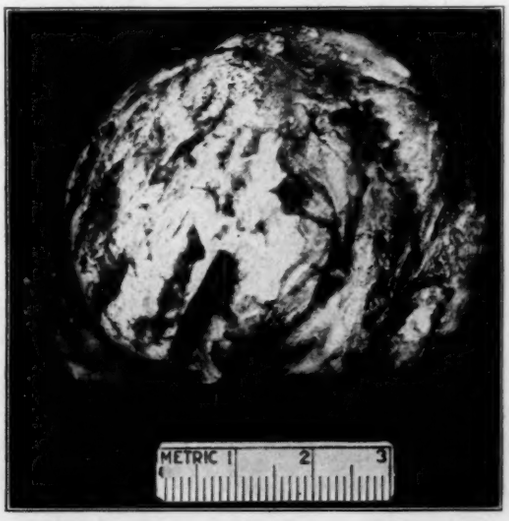

Fig. 5 (case 2).—Osteoma removed from mastoid process.

DR. HARRINGTON B. GRAHAM, San Francisco: I had occasion recently to see a patient with an extremely large tumor involving both frontal sinuses. The interesting part of this case is that I saw him in 1931. Comparing his roentgenograms at that time with those of the present affords a definite idea of the rapidity of growth of one of these tumors. The lesion at that time appears to have been about one fifth the size of the present growth. The difficulty in operating in these cases has been described by the author. In my case only one thing could be done and that was to remove the anterior wall of the frontal sinus. This wall proved to be very thin and was easily dis-

posed of. The tumor was discrete but was so large that it compelled me to divide it into two parts by chiseling through the center. After one half of the tumor had been removed it was possible to elevate the other half without injuring the posterior wall of the sinus. There were three distinct tumors lying in the left orbit which were not connected with the mother growth and I find from the literature that this is not an unusual condition; these separate tumors seemingly have their own blood supply and are found frequently in the soft tissues. Since Dr. Carmody's work there have been a good many cases added to the literature, especially from Hungary, where considerable work has been done on the pathology.

PATHOLOGIC CHANGES IN AMBLYOPIA FOLLOWING TRYPARSAMIDE THERAPY

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IOWA CITY

The pentavalent arsenical atoxyl, introduced in 1902 by Blumenthal,[1] was first used in the treatment of protozoan diseases in 1905 by Thomas.[2] Since, as the name indicates, the drug was considered nontoxic, it was used extensively in the therapy of trypanosomiasis, pernicious anemia and psoriasis. After the identification of Spirochaeta pallida, the drug was almost immediately applied to the treatment of syphilis. Extensive use of atoxyl soon demonstrated various cases of toxicity. Progressive loss of vision occurred frequently (Bornemann,[3] Igersheimer,[4] Beck,[5] Fehr[6]), and studies of the visual fields showed that the subjective blurring of vision was accompanied by peripheral contraction that progressed to complete blindness. Once visual symptoms occurred, visual loss continued in spite of withdrawal of the drug. Loss of vision developed in nonsyphilitic as well as syphilitic patients, and it appeared that the drug acted specifically on the visual sensory mechanism.

In 1907 Ehrlich's[7] studies in chemotherapy led to the discovery of arsacetin, a less toxic substitution product of atoxyl. The new drug was used only a short time, since clinical experience demonstrated that it also had a deleterious effect on vision (Sattler,[8] Hammes,[9] Iversen,[10] Ruete[11]). The hope for a nontoxic pentavalent arsenical led to the introduction of tryparsamide by Lorenz and Loevenhardt.[12] Once more clinical application showed that the new drug, although less toxic than atoxyl or arsacetin, also caused deterioration of vision and optic atrophy (Woods and Moore,[13] Neff,[14] Cady and Alvis,[15] Fine and Barkan,[16] Mayer[17]). With tryparsamide, however, visual injury was less common, and improvement or at least a cessation of the toxic process occurred when administration of the drug was discontinued. Recent reports have adequately reviewed the clinical use and toxicity of tryparsamide.

Although the toxicity of the pentavalent arsenicals has been investigated by a number of authors, no satisfactory explanation for the visual pathologic changes has been determined. The toxic action of atoxyl, arsacetin and tryparsamide appears to have a special affinity for the visual system, for general symptoms most frequently do not accompany the ocular manifestations. Young and Loevenhardt,[18] after experimental comparison, concluded that the aniline group in the ortho position contribute to the toxic effects of these compounds and that the pentavalent arsenic is only a secondary consideration. An indication that the visual loss is not due to arsenic or the aniline molecule of the drugs is that these substances when toxic to the visual system ordinarily cause a defect in the central field, while atoxyl and tryparsamide almost invariably cause concentric contraction of the visual fields. Furthermore, the disintegration of pentavalent arsenicals in the blood stream is very slow. From a quantity of the drug injected, arsenic is gradually split off; some of the drug remains (Igersheimer and Rothman[19]) in the blood and tissues, while a large portion is excreted unchanged in the urine. Young and Muehlenberger[20] considered the possibility of accumulation of tryparsamide as the cause of toxic effects. Igersheimer[4] expressed the opinion that atoxyl itself or a reduction product of it acts directly on the cell. He stated also that the eye has a high affinity for the atoxyl molecule but not for arsenic. According to Meyer and Gottlieb[21] arsenic can be demonstrated in animal eyes after poisoning with atoxyl but it cannot be identified after poisoning with arsenic. In their experiments the arsenic poisoning did not cause blindness. Osborne[22]

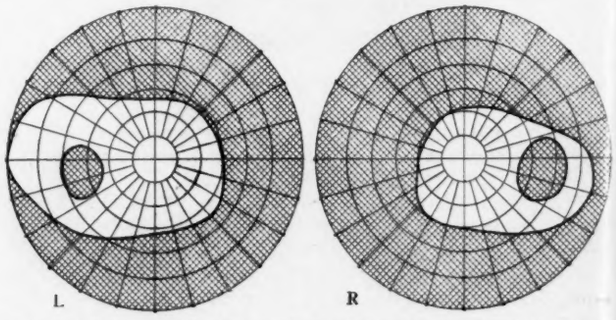


Fig. 1.—Visual fields taken prior to injection of tryparsamide; 2/1,200 tangent screen.

From the Department of Ophthalmology, State University of Iowa College of Medicine.

Read before the Section on Ophthalmology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 15, 1938.

1. Blumenthal, quoted by Meyer, H. H., and Gottlieb, R.: Experimental Pharmacology, translated by V. E. Henderson, Philadelphia, J. B. Lippincott Company, 1926, p. 565.
2. Thomas, H. W.: Some Experiments in the Treatment of Trypanosomiasis, Brit. M. J. **1**: 1140, 1905.
3. Bornemann, W.: Ein Fall von Erblindung nach Atoxylininjectionen bei Lichenruber, München. med. Wchnschr. **52**: 1043, 1905.
4. Igersheimer: Ueber die Wirkung des Atoxyls auf das Auge, Arch. f. Ophth. **71**: 379, 1909.
5. Beck, Max: Ueber sehstörung bei Schlafkranken in Verlauf der Atoxylbehandlung, Zentralbl. f. prakt. Augenh. **33**: 129, 1909.
6. Fehr: Sehnervenerkrankung durch Atoxyl, Deutsche med. Wchnschr. **33**: 2032, 1907.
7. Ehrlich, Paul: Chemotherapeutische Trypanosomen Studien, Berl. klin. Wchnschr. **44**: 341, 1907.
8. Sattler, C. H.: Pathologisch-anatomische Untersuchung eines Falles von Erblindung nach Arsacetininjectionen, Arch. f. Ophth. **81**: 546, 1912.
9. Hammes, F.: Zur Beurteilung des Arsacetins und seiner Einwirkung auf den Sehnerven, Deutsche med. Wchnschr. **36**: 267, 1910.
10. Iversen, J.: Ueber die Behandlung russischen Recurrens mit Arsacetin, München. med. Wchnschr. **56**: 1785, 1909.
11. Ruete: Ein Fall von Sehnervenerkrankung nach Arsacetininjectionen, München. med. Wchnschr. **56**: 718, 1909.
12. Lorenz, W. F., and Loevenhardt, A. S.: The Therapeutic Use of Tryparsamide in Neurosyphilis, J. A. M. A. **80**: 1497 (May 26) 1923.
13. Woods, A. C., and Moore, J. E.: Visual Disturbances Produced by Tryparsamide, J. A. M. A. **82**: 2105 (June 28) 1924.
14. Neff, E. E.: Effect of Tryparsamide on the Optic Tract: A Chemical Study, Wisconsin M. J. **24**: 569 (Aug.) 1925.
15. Cady, L. D., and Alvis, B. Y.: The Uses of Tryparsamide in Patients With and Without Ocular Lesions, J. A. M. A. **86**: 184 (Jan. 16) 1926.
16. Fine, Max, and Barkan, Hans: Prevention of Ocular Complications in Tryparsamide Therapy, Am. J. Ophth. **20**: 45 (Jan.) 1937.
17. Mayer, Leo L.: Tryparsamide Therapy of Neurosyphilis and Atrophy of the Optic Nerve, J. A. M. A. **109**: 1793 (Nov. 27) 1937.
18. Young, A. G., and Loevenhardt, A. S.: The Relation of the Chemical Constitution of Certain Organic Arsenical Compounds to Their Action on the Optic Tract, J. Pharmacol. & Exper. Therap. **23**: 107 (March) 1924.
19. Igersheimer and Rothman, quoted by Meyer and Gottlieb,[1] p. 566.
20. Young, A. G., and Muehlenberger, C. W.: The Excretion of Tryparsamide, J. Pharmacol. & Exper. Therap. **23**: 461 (July) 1924.
21. Meyer and Gottlieb,[1] p. 566.
22. Osborne, E. D.; Putnam, E. D., and Hitchcock, B. S.: The Effect of Arsenic on Rabbits, Arch. Dermat. & Syph. **25**: 419 (March) 1932.

showed that arsenic in moderate amounts can be identified in the rabbit brain after therapeutic doses of tryparsamide.

Although numerous cases of tryparsamide amblyopia have been observed clinically there have appeared no reports of histologic examination of the eyes and optic pathways in such cases. Reports of pathologic changes in amblyopia following the use of atoxyl were made by Nonne [23] and Birch-Hirschfeld [24] and following the use of arsacetin by Sattler.[8] Nonne observed atrophy in the optic nerves, chiasma and tracts obtained from a patient who died several weeks after blindness occurred. A clinical recognition of optic atrophy had been made before death. In Birch-Hirschfeld's case a complete examination was made of a man who died two years after the beginning of administration of atoxyl and twenty-two months after complete loss of vision. The atoxyl was used in the treatment of psoriasis. His study disclosed degeneration of the third neuron, chromatolysis, disintegration of the retinal ganglion cells and gliosis of the retina. Some nuclei of the inner nuclear layer appeared faded. The peripheral portion of the outer nuclear layer contained many shrunken nuclei. There was almost total degeneration of the optic nerves but no evidence of inflammation. The ganglion cells of the lateral geniculate bodies also showed degeneration. After injection of atoxyl in experimental animals Birch-Hirschfeld [24] was able to demonstrate a similar condition. Changes in retinal ganglion cells were observed in the cat, and extensive chromatolysis was observed as early as nine and one-half days after injection in a dog. In some dogs he observed changes in the occipital cortex and geniculate bodies. He said that the retina was most susceptible to the poison but that the condition behaved like a purely degenerative process of the medullary sheaths of the optic nerves. Sattler described the pathologic changes in a case of amblyopia following treatment of pernicious anemia with arsacetin. Loss of vision began six weeks after the beginning of treatment and progressed to total blindness in an additional six weeks. Death occurred five weeks later. There were no demonstrable changes in the first neuron, but a shrinkage or a swelling of a few cells in the inner nuclear layer was seen. The greatest damage was to the retinal ganglion cell layer and the optic nerve. Gliosis and reduction in the number of the ganglion cells were reported. The ganglion cell nuclei were shrunken or had lost their sharp margins, and the Nissl substance was not visible. The greatest degree of myelin disintegration occurred in the anterior portion of the optic pathway. More recently Sattler [25] expressed the opinion that although one would expect the process to be primary in the retina it is possible that the processes in the nerve fiber and the retina advance at the same time. A striking fact concerning all the reports of pathologic changes is the absence of evidence of tissue changes outside the eye and the optic pathways, for the remainder of the organs and the central nervous system show no evidence of a related pathologic process.

These observations of the pathologic changes in amblyopia occurring after the administration of compounds containing pentavalent arsenic were made at a time remote from the onset of blindness. A complete study of a case in which pathologic material was obtained nine days after the administration of 1 Gm. of tryparsamide and seven days after the onset of visual disturbances is presented:

A white man aged 52 was admitted Aug. 13, 1937, because of inability to walk. This manifestation, together with difficulty in control of the bladder, had begun two years previously. There was a history of gonorrhea in 1907. The examination showed 6/6 vision in each eye. The pupils were round and equal and reacted promptly and effectively in near accommodation, but the reaction to light was sluggish. Ophthalmoscopic examination revealed early optic atrophy of the primary type on both sides; the visual fields (fig. 1) showed contraction with a 2/1,200 mm. target on the tangent screen. The blood pressure was 140 systolic and 86 diastolic, there was a cord bladder, the patient was unable to walk and the Wassermann reactions of the spinal fluid and blood were 4 plus.

On August 16, 1 Gm. of tryparsamide was administered intravenously. On the morning of August 18 a cystoscopic examination was made and was followed by chills, vomiting and fever, the temperature reaching 103 F. During the afternoon of that day the patient complained of blurring of vision. The following morning there was no subjective central or peripheral vision, but the pupils responded sluggishly to light, as at the time of admission. The ophthalmoscope revealed no change in the appearance of the nerve heads or fundi. On August 20 blindness persisted, but no pupillary response to light could be elicited. The pupils were smaller than at previous examinations. The general condition of the patient failed progressively. Further external examination of the eyes disclosed no pupillary light reaction, and no new changes developed in the fundus. The urea nitrogen content rose to 130.9 with a creatinine content of 11.5, and death from uremia occurred on the morning of August 25. A complete necropsy was begun two hours after death.

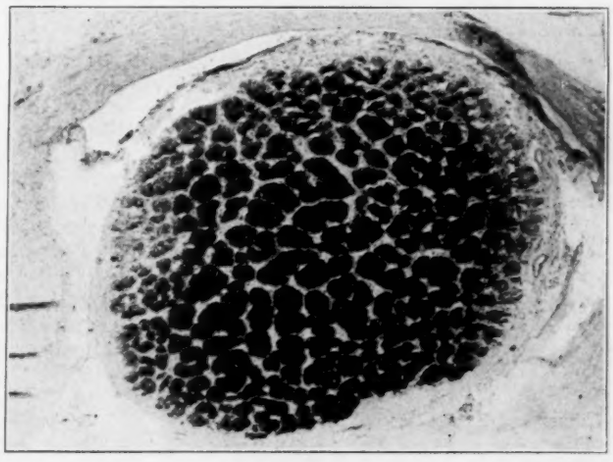


Fig. 2.—Optic nerve. Old peripheral degeneration is evident; Held stain.

General pathologic examination was made by Dr. H. P. Smith, head of the department of pathology. He reported that the liver showed no evidence of necrosis. The cells in the central part of each lobule showed fat droplets and fine brown pigment granules. The kidneys were markedly reduced in size (weighing 90 Gm. each), but the renal pelves were distended. Histologically there were extreme changes of a chronic nature that had destroyed the tubules and hyalinized the glomeruli. The stroma between the tubules was involved in an extensive chronic inflammatory process. Although the pathologic changes were compatible with those of chronic nephritis, the inflammation and dilatation of the renal pelves indicated the presence of pyelonephritis. There was no evidence of acute change. The pathologist believed that the patient had been on the verge of uremia for some time and that very little additional injury was necessary to bring about a critical change. Additional postmortem diagnoses were bronchopneumonia and meningovascular syphilis.

23. Nonne, M.: Anatomische Untersuchung eines Falles von Atoxylblindung, Med. Klin. **4**: 757, 1908.
24. Birch-Hirschfeld, A., and Koster, G.: Die Schädigung des Auges durch Atoxyl, Arch. f. Ophth. **76**: 403, 1910.
25. Sattler, C. H., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1932, vol. 7, p. 251.

The posterior segment of each eye was fixed in absolute alcohol and acetic acid according to Nissl's technic for study of the retinal ganglion cells. Pieces of the nerves and tracts were fixed in osmic acid, Marchi, and solution of formaldehyde for hematoxylin and eosin, silver, and Held stains. Portions of the occipital cortex and the lateral geniculate bodies were placed in 10 per cent solution of formaldehyde in preparation for hematoxylin and eosin, and Nissl stains.

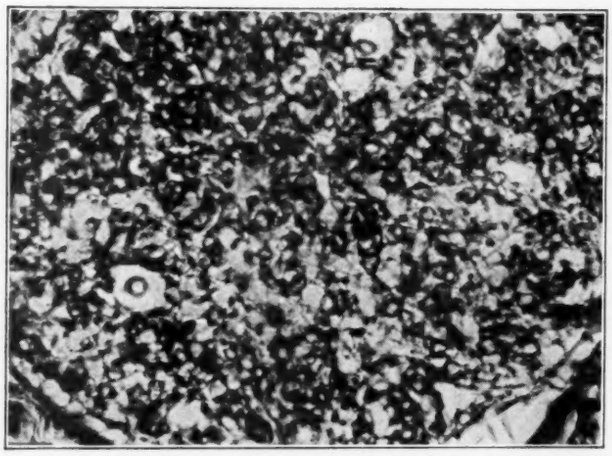


Fig. 3.—High power view of normal medullary sheaths of optic nerve; osmic acid stain.

The occipital cortex and the lateral geniculate bodies showed no evidence of injury to the cell bodies, and the topography of the regions was normal. There was neither chromatolysis nor disturbance of the nuclei. Fatty granules were observed in the cytoplasm of the cells of the lateral geniculate body and other regions, but these changes are considered physiologic in a person of this age.

The optic tracts posteriorly showed little evidence of change with the Held stain. Small areas of gliosis indicated the presence of an old atrophic process, but the osmic acid and Marchi preparations revealed no evidence of acute demyelinating disease. In the anterior portion of the optic tracts the changes were similar but the amount of gliosis was more definite. Staining of the axis cylinders with silver proved them to be intact.

The periphery of both optic nerves showed gliosis and old disintegration of the myelin sheaths that appeared in proportion to the visual field changes (fig. 2). No areas of inflammatory reaction were observed, and the nerve sheaths were of normal appearance. Osmic acid (fig. 3) and Marchi preparations showed no evidence of acute degeneration in the optic nerves.

Within the retina there was gliosis in the nerve head and retina consistent with the antemortem diagnosis of early optic atrophy. Low power microscopic examination of the retina showed a normal morphologic appearance, with the several layers distinctly discernible. Ganglion cells were present in abundance. Examination with the high power objective disclosed the rods and cones in a good state of preservation. The rod and cone nuclei appeared entirely normal. In the posterior segment of the eye the cells of the inner nuclear layer were for the most part normal, but in places cells of the innermost row appeared faded and almost homogeneous (fig. 4). The general nuclear morphologic appearance could be made out, but no evidence of a chromatin network or of cytoplasmic structure could be recognized. The appearance was that of ghost cells. In the central region of the globe these cells were occasionally seen, but as one passed toward the periphery their occurrence was more frequent. The ganglion cells were numerous, but the morphologic appearance was profoundly changed (fig. 5). The cells were irregular in outline, and the cytoplasm in some cells was cloudy while in others it had a foamy appearance. In most of the ganglion cells the Nissl substance had entirely disappeared, but a peripheral rim of Nissl granules was recognized in a few cells. The ganglion cell nuclei were variable. Some were large, homogeneous and apparently swollen, while in some cells a faint indication of a chromatin net remained, and a few cells contained a nucleolus. Many glial cells were present in the ganglion cell and nerve fiber layers. The nuclear changes and the loss of Nissl substance indicate a profound cellular reaction similar to that seen in the central nervous system after acute intoxications.

COMMENT

The reports of pathologic changes occurring after the use of atoxyl (Birch-Hirschfeld) and arsacetin (Sattler) show several results similar to those here reported for tryparsamide. Both observers recognized changes in the ganglion cells and in the inner nuclear layer of the retina as well as degeneration of the nerve fibers of the optic nerve. In experimental work, however, Igersheimer was unable to find any evidence of change in the ganglion cells of the retina of the cat or dog, but Birch-Hirschfeld's animals showed abnormalities similar to those observed in his reported case. The pathologic state in the cases recorded differs from that in the present case, since in the previous cases the process had gone on to a chronic stage. Histologic examination immediately after administration of the pentavalent arsenicals and the development of amblyopia has not previously been reported.

The present study presents observations in agreement with previous reports in regard to the changes in the ganglion cells and in the inner nuclear layer, but evidence of acute primary degeneration of nerve fiber in the optic pathways was not present. It seems apparent that changes in the optic nerves, tracts and lateral geniculate bodies must be of a secondary nature; no evidence of acute change could be observed in these situations nine days after the administration of the drug, yet definite evidence of cellular change was observed in the ganglion cells of the retina. It seems probable that the amblyopia following the administration of tryparsamide, similar to that due to tobacco and

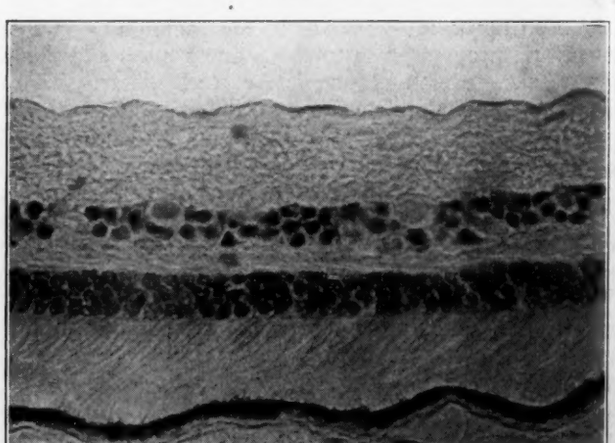


Fig. 4.—Peripheral part of retina. Two "ghost" cells are seen in the inner nuclear layer; Nissl stain.

alcohol, is caused by a primary degeneration of the ganglion cells of the retina and that there ensues a secondary degeneration of the nerve fibers and myelin sheaths. The significance of the changes in the inner nuclear layer is not known. It is possible that in less extensive injury these cells are most affected, and their degeneration results in the peripheral contraction of the visual field.

Birch-Hirschfeld expressed the opinion that arteriosclerosis or alcoholism might play a part in the causation of the condition. In this case neither of these con-

ditions was present. Accumulation of the drug has been held responsible for the pathologic changes, yet this patient received a single injection. Previous experience with tryparsamide amblyopia has demonstrated that, if ocular complications are to develop, evidence of the change usually occurs early in the treatment. In one of Birch-Hirschfeld's experimental animals extensive chromatolysis was observed nine and one-half days after the beginning of treatment, and the author ventured the opinion that the animal was idiosyncratic to the drug. Lillie [26] suggested an idiosyncrasy as the underlying cause of the amblyopia. The fact that the patient reported had extensive changes after a single injection of 1 Gm. of tryparsamide lends credence to this view.

SUMMARY

1. Acute degeneration of the retinal ganglion cells was observed nine days after injection of 1 Gm. of tryparsamide and seven days after the onset of blindness.

2. Acute degeneration of cells in the innermost portion of the inner nuclear layer was present.

3. Evidence of acute primary degeneration in the optic nerves and tracts was not present.

4. General pathologic changes due to arsenic poisoning were not observed.

ABSTRACT OF DISCUSSION

DR. FREDERICK C. CORDES, San Francisco: Dr. Leinfelder's report is the first histologic study of tryparsamide amblyopia. Certain observations were rather striking. The changes in the ganglion cells and innermost layers of the inner nuclear layer were very definite, especially in the periphery of the retina. The fact that the neuro-epithelial layer was not involved was also noteworthy. Of particular interest was the fact that examination of the occipital cortex, lateral geniculate bodies, optic tracts and nerves failed to reveal any evidence of acute inflammation or degeneration. The changes present in the optic nerve were those of an old process, easily accounted for by the preexisting optic atrophy. The changes noted in the retina have been observed in acute poisoning from methyl alcohol, ethyl alcohol, quinine, nicotine and atoxyl. Lillie and others have contended that the occasional cases of tryparsamide amblyopia reported have been primarily the result of idiosyncrasy to the drug. The fact that 1 Gm. of the drug produced such marked changes would tend to confirm this opinion. Clinical observation has shown that, aside from the subjective symptoms, the earliest changes are those of contracted field and not visible changes in the optic disk. The fact that the greatest changes were found in the periphery of the retina and that no acute changes were found in the optic nerve emphasizes the importance of careful field studies early in the course of therapy. The greatest controversy in tryparsamide therapy has centered around its use in the presence of optic atrophy. Last year Dr. Mayer presented a paper before this section on tryparsamide therapy which bore out his contention that tryparsamide was not contraindicated in optic atrophy. Dr. Leinfelder's report seems to confirm this. If the effect of tryparsamide in a sensitive person was primarily on the optic nerve and tracts, one would expect to find signs of acute degeneration or inflammation in these structures, especially in view of the fact that the eye was examined so soon after administration of the drug. Lorenz and Loevenhardt, in introducing the drug, warned against its use "in cases showing degenerative changes in the retina." The fact that the acute changes in the histologic report presented were limited to the retina should make us extremely cautious in advising the use of the drug in the presence of pathologic changes in the retina. Dr. Leinfelder's paper is an important contribution to the subject of tryparsamide therapy.

26. Lillie, W. I.: Peculiar Contraction of the Normal Fields Associated with Syphilis of the Cerebral Nervous System, Tr. Am. Ophth. Soc. **32**: 153-163, 1934.

DR. MAX FINE, San Francisco: It is unfortunate that the picture was somewhat confused by the presence of an early optic atrophy in Dr. Leinfelder's patient. There is general agreement, however, that tabetic optic atrophy begins in the intracranial portions of the optic nerve. The absence of extensive atrophy in the optic nerves in the presence of marked degenerative changes in the ganglion cell and inner nuclear layers suggests that the process involved is one other than tabetic optic atrophy. A striking feature of the sections Dr. Leinfelder has exhibited is the relative integrity of the central portion of the retina and the progressively severe changes as the periphery is approached. These observations correspond in a rough manner to the peripheral constriction of the visual field in cases of tryparsamide amblyopia. The delayed appearance of optic atrophy in tryparsamide amblyopia, even when the field changes are severe, fits in with Dr. Leinfelder's conclusion that the degeneration occurs first in the inner nuclear layer. The ocular complications from tryparsamide may be divided for clinical purposes into two groups: One shows the usual reaction consisting of preliminary symptoms of blurring, followed by a depression of the peripheral field with relative sparing of the temporal field. The process is reversible if tryparsamide is discontinued early, when the field changes are not too far advanced. The second type of reaction, of more infrequent occurrence, is an acute intoxication in which the patient may go to complete blindness within forty-eight hours after a single injection of tryparsamide. This reaction is much less reversible. There may be a degree of recovery, but usually there is severe permanent damage. I have seen three such patients who became almost totally blind after the first or second injection of tryparsamide. Each of these patients had an early primary optic atrophy before the institution of tryparsamide therapy. Dr. Leinfelder's case appears to fall into this group. The occurrence of more than 90 per cent of reactions with the first five injections speaks against a cumulative effect in the ordinary sense. Young and Meuhlenberger have shown through studies of urinary arsenic that whereas a great majority of persons excrete 95 per cent of the arsenic within twenty-four hours, a small number excrete the drug much more slowly, and in one instance arsenic was recovered from the urine after three weeks.

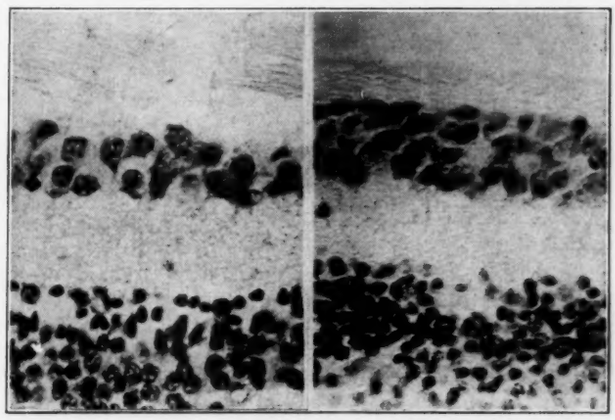


Fig. 5.—Normal retina and ganglion cells are shown on the left. Acute degeneration of ganglion cells of the retina after injection of tryparsamide is seen on the right; Nissl stain.

DR. JOHN E. WEEKS, Portland, Ore.: I have been interested in this subject because I have seen two cases of amblyopia from the use of tryparsamide. In neither was there any intimation of impairment of vision before the tryparsamide was administered. Both were cases of syphilis of long standing. In the first case three doses were given at five day intervals; the first two were small, the third a dose of 1.5 Gm. The vision on the second day after the last dose was impaired. The fundi showed almost no change. Vision of one eye was reduced to 22/100, of the other eye to 20/70. The fields of vision were narrowed concentrically in both eyes, about 15 degrees in one eye and 25 degrees in the other. The blood vessels were somewhat reduced in size. There was no exuda-

tion and no hemorrhage, but the temporal portions of the disks were a bit pale. Vision of 20/20 was recovered in both eyes, but moderate concentric limitation of the fields persisted. In the second case, tryparsamide had also been injected once before the second dose, from which the amblyopia followed, was given. The second dose was 1.5 Gm. given intravenously. The patient became totally blind in twenty-four hours. An ophthalmologist who examined him could not detect that he had any vision whatever. The fundi in this case were similar to the fundi in the other case. I saw the patient in the afternoon of the day of his complete blindness, at which time the right iris reacted slightly to the stimulus of light but not the left. However, within a week the vision was greatly improved and the field of vision was very much contracted. Eventually the patient obtained a field of vision of only about 20 degrees in each eye but a visual acuity of 20/20. I regard the use of tryparsamide as something that should be undertaken only after careful tests regarding the susceptibility of the patient to tryparsamide have been made. There is a widespread opinion that, wherever there is any atrophy of the optic nerve or any disturbance of the fundus from syphilis, tryparsamide should not be employed. This amblyopia corresponds to some extent to that of quinine amblyopia, but the use of tryparsamide has caused permanent total blindness in a few cases. No case of complete permanent blindness from quinine is on record.

DR. OTIS A. SHARPE, San Francisco: A man aged 25 was being treated for syphilis with tryparsamide. He was referred to me one morning for visual fields. He complained of some indefinite disturbance in the fields. I took the fields, and there was about 10 or 15 degrees concentric contraction. The vision was 20/15 in each eye. I advised discontinuance of the treatment. The next morning I was called to the ward, where it was reported that he had gone completely blind. When I first examined the background there was no visible change. The next morning, which was less than twenty-four hours, the man was completely blind; there were no changes in the backgrounds to be seen. There was a very slight reaction of the pupils to light. Five years later this man appeared in my office and wanted a report from me. I examined his eyes and the background showed perfectly white disks. He took the case to court, claiming that the tryparsamide was the cause of his blindness. The other side claimed it was syphilitic optic atrophy. I reported this because of the short time in which complete blindness developed.

DR. FREDERICK H. VERHOEFF, Boston: At the present time it seems to me to be of no practical importance whether tryparsamide or other arsenicals in producing blindness affect primarily the optic nerve or the retinal ganglion cells, but of course the question is of great scientific interest and may become of practical importance. I haven't the slightest doubt that Dr. Leinfelder has shown in this case that the ganglion cells were markedly affected, but I do not feel sure that they were primarily affected. It seems to me, in spite of the fact that histologically there was no evidence that the nerve fibers were affected, that it was perfectly possible that they may have been affected to such an extent as to produce changes in the ganglion cells. This question has arisen in connection with many toxic agents and in my opinion has seldom if ever been satisfactorily answered.

DR. EDWARD JACKSON, Denver: Bearing on the point that has been brought up by Dr. Verhoeff, many years ago I was consulted by a young man with very marked macular changes. There were some slight hemorrhages and a good deal of haziness in the macula. One of the first questions I asked him was whether there was any history of blindness or partial blindness in his family. He stated that absolutely there had been none; but two years after that Dr. George M. Gould, who knew the family, reported it as a case of Leber's disease, which without any doubt it was. I saw it at a very early stage, and the appearance of the retina seemed to point out what one would expect, that the nutrition of the ganglion cells in the macula was affected before the nerve fibers proceeding from that cell showed any sign of change. There was no signs at first of disease in the optic disks. It ran the course of Leber's disease.

DR. P. J. LEINFELDER, Iowa City: Dr. Verhoeff's question concerning whether the ganglion cells were primarily affected or the nerve fibers I think can be definitely answered. Although neurohistologic technic is by no means infallible, research that I have done with the optic nerve has shown conclusively that, if one sections or injures the optic nerve, pathologic changes are observable with the osmic acid and the Marchi methods as early as three days following the injury. Furthermore, the neurofibrils show disintegration within ten days. I think it is striking that in this case there were absolutely no evidences of acute degeneration in the nerve fiber of the optic nerve even close to the eyeball. Dr. Sharpe mentioned pupillary reactions. It is conspicuous in the literature that pupillary reactions are at first retained in spite of the subjective blindness. Dr. Weeks brings up two questions. One is whether the fundus was changed. I did not mention it in my primary discussion but, throughout the nine days following the injection of the tryparsamide, no changes in the fundus over those that were first observed were noted. There was no change whatever from the optic atrophy. As for patients who recover their vision, it is astounding to note the amount of reversible change that can occur in the ganglion cells of the retina following injury to the optic nerve or tracts. Extensive chromatolysis of the ganglion cells in the retina occurs early, yet a large percentage of these cells recover at a later date. This was demonstrated by Birch-Hirschfeld in 1900. Dr. Fine inquires concerning histologic differences between the nasal and temporal segments of of the retina. I would not attempt an evaluation of such a thing on the histologic material available for one would need to make a great many calculations that would not yield any definite, usable data.

THE GORDON TEST FOR HODGKIN'S DISEASE

A REACTION TO EOSINOPHILS

JAMES B. McNAUGHT, M.D.
SAN FRANCISCO

In 1932 Gordon [1] reported that intracerebral inoculation of rabbits and guinea pigs with suspensions of lymph nodes from patients with Hodgkin's disease was followed in several days by an encephalitic syndrome of characteristic pattern. This was typified by early muscular rigidity, progressive incoordination, ataxia and spastic paralysis of the hind limbs, accompanied by loss of weight and subnormal temperature. Tissue suspensions from patients with acute Hodgkin's disease often produced in addition to these changes retraction of the head, opisthotonos and convulsive seizures, and the animals frequently died within a few days to a month. In the less severe type of reaction the animals passed into a chronic state with marked muscular atrophy and wasting. Gordon obtained these reactions with suspensions from nineteen of twenty patients with Hodgkin's disease and with none of forty-one control suspensions. He concluded from his studies of the properties of the pathogenic agent that it was undoubtedly a virus and was the primary causative agent of Hodgkin's disease. He proposed the biologic test as a specific one for the practical diagnosis of Hodgkin's disease.

From the Department of Pathology, Stanford University School of Medicine.

Supported in part by the Rockefeller Fluid Research Fund of the School of Medicine of Stanford University.

Read before the Section on Pathology and Physiology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 16, 1938.

1. (*a*) Gordon, M. H.: Rose Research on Lymphadenoma: Studies on the Aetiology of Lymphadenoma, Bristol, England, John Wright & Sons, Ltd., 1932; (*b*) Hodgkin's Disease: A Pathogenic Agent in the Glands, and Its Application in Diagnosis, Brit. M. J. **1**: 641 (April 15) 1933.

The Gordon test has been applied in 179 cases of Hodgkin's disease by various investigators [2] and found positive in 124 (69.3 per cent). In 210 of 214 control experiments (98.1 per cent), with suspensions of lymph nodes from normal patients and from patients with hyperplasia, adenitis, leukemia, tuberculosis, carcinoma and sarcoma, the test was negative. These results indicate that while the Gordon test is only 70 per cent accurate in detecting Hodgkin's disease it apparently is highly specific in distinguishing this condition from other dyscrasias of the lymph nodes.

Gordon [3] persists in his belief that the causal agent of Hodgkin's disease is elementary virus bodies, and he has recently employed emulsions of his sensitized elementary bodies, recovered from the lymph nodes of patients with active Hodgkin's disease, in treating this condition. Warner [4] reported beneficial results following the use of Gordon's sensitized emulsions in cases of early Hodgkin's disease. Other investigators [5] have been dubious of the virus nature of the active agent in the Gordon test. They have based their skepticism on the observation that although the pathogenic agent is definitely filter passing and the disease produced in animals bears some of the characteristics of an infectious process the agent has not been cultivated in vitro nor has its passage from animal to animal been accomplished. Gordon reported that rabbits recovering from an initial paralysis were immune to a second inoculation of active material, but other investigators [6] found such rabbits just as susceptible as the control animals.

Friedemann and Elkeles [7] reported that intracerebral inoculation of rabbits with extracts of normal and pathologic human bone marrow, spleen and leukocytes produced a paralysis indistinguishable from that caused by the agent which Gordon discovered in glands from patients with Hodgkin's disease. They expressed the opinion that their active agent could not possibly be a living virus since it withstood extracting treatment which no living virus or bacteria could be expected to tolerate. In support of this theory Kelser and King [5] submitted tissues containing known neurotropic viruses of St. Louis encephalitis, equine encephalomyelitis and rabies to the extraction processes used on the leukocytic material, and in all instances the viruses were rendered inert. Friedemann suggested that the encephalitogenic agent of Hodgkin's disease and that in the spleen, bone marrow and leukocytes are of the nature of a proteolytic enzyme such as that demonstrated by Jochmann and Lockemann [8] in 1908. The active agent was not found in all bone marrows or all specimens of pus.[9] MacKenzie and Van Rooyen [10] confirmed much of the work of Friedemann but found no relation between the proteolytic activity and the encephalitogenic property of the agent and thus did not identify it with Jockmann's proteolytic enzyme.

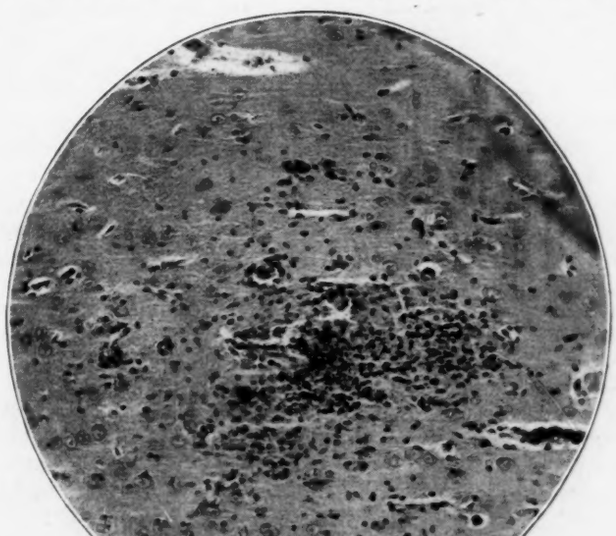


Fig. 1.—The inoculation area in the cerebral cortex of a paralyzed rabbit (slightly reduced from a photomicrograph with a magnification of 160 diameters).

It is obvious that, in some marrow, leukocytes, pus and spleens as well as some lymph nodes from patients with Hodgkin's disease there is an active substance capable of producing a characteristic paralysis in certain experimental animals. Turner, Jackson and Parker [2n] recently published convincing evidence showing that the active agents of Gordon and of Friedemann are derived from the eosinophil and consequently are most probably identical. This evidence is in accord with my observations on the Gordon test, covering a period of several years, herewith presented.

METHODS

The procedures of Gordon [1a] have been followed in the performance of the tests. With sterile technic, human lymph nodes obtained either at biopsy or at

2. These include:
(*a*) Van Rooyen, C. E.: A Biological Test in the Diagnosis of Hodgkin's Disease, Brit. M. J. **1**: 644 (April 15) 1933.
(*b*) Van Rooyen, C. E.: Some Properties of the Encephalitogenic Agent in Lymphadenomatous Tissue, Brit. M. J. **1**: 519 (March 24) 1934.
(*c*) Van der Hoeden, J., and Hulst, L. A.: De Ziekte van Hodgkin en die Proef van Gordon, Nederl. tijdschr. v. geneesk. **78**: 4305, 1934.
(*d*) Dassen, R.; Fisher, A., and Fustinoni, O.: La prueba de Gordon en el diagnostico de la linfogranulomatosis maligna, Rev. Asoc. méd. argent. **48**: 1397 (Dec.) 1934.
(*e*) Davis, W. B.: Hodgkin's Disease, Brit. M. J. **1**: 324 (Feb. 16) 1935.
(*f*) D'Ovidio, F. R., and Vucetich, Martin: Sobre un caso de enfermedad de Sternberg Hodgkin, Rev. Asoc. méd. argent. **49**: 372 (March) 1935.
(*g*) Manson, M. H.: Biological Phenomena in Hodgkin's Disease, Minnesota Med. **18**: 263 (April) 1935.
(*h*) Bortolozzi, Menenio: Linfogranuloma e reazione biologica di Gordon, Diag. e tec. di lab. **6**: 273 (April) 1935.
(*i*) Smith, E. C.: Hodgkin's Disease in Natives of Nigeria, Lancet **2**: 874 (Oct. 19) 1935.
(*j*) Rosenberg, D. H., and Bloch, Leon: The Gordon Test for Hodgkin's Disease, J. A. M. A. **106**: 1156 (April 4) 1936.
(*k*) Goldstein, J. D.: The Gordon Test for Hodgkin's Disease, Am. J. M. Sc. **191**: 775 (June) 1936.
(*l*) Chapman, E. M.: Studies in Hodgkin's Disease, Ann. Int. Med. **10**: 742 (Dec.) 1936.
(*m*) Wurm, K.: Zur Frage des Gordontestes bei der Hodgkinschen Lymphogranulomatose, Verhandl. de deutsch. Gesellsch. f. inn. Med. **49**: 228, 1937.
(*n*) Turner, J. C.; Jackson, Henry, Jr., and Parker, Frederic: The Etiological Relation of the Eosinophil to the Gordon Phenomenon in Hodgkin's Disease, Am. J. M. Sc. **195**: 27 (Jan.) 1938.
(*o*) Gordon.[1]

3. Gordon, M. H.: Aetiology of Lymphadenoma: Sensitized Vaccine of the Elementary Bodies, Lancet **2**: 65 (July 11) 1936.

4. Warner, E. C.: The Treatment of Lymphadenoma with a Sensitized Vaccine of the Elementary Bodies, Lancet **2**: 417 (Aug. 22) 1936.

5. Kelser, R. A., and King, L. S.: Studies of a Paralysis Syndrome Produced in Rabbits and Guinea Pigs by Extracts of Normal Primate Bone Marrow, Am. J. Path. **12**: 317 (May) 1936. Van Rooyen, C. E.: The Interpretation and Significance of Gordon's Test in the Diagnosis of Hodgkin's Disease, Edinburgh M. J. **44**: 455, 1937. Chapman.[2l] Wurm.[2m] Turner, Jackson and Parker.[2n]

6. Uhlenhuth, P., and Wurm, K.: Zur Frage der Hodgkinschen Lymphogranulomatose, Klin. Wchnschr. **15**: 1025 (July 18) 1936. Van Rooyen.[2b] Chapman.[2l]

7. (*a*) Friedemann, Ulrich, and Elkeles, A.: Studies on the Aetiology of Blood Diseases: A Pathogenic Agent in Normal Human Bone Marrow, Brit. M. J. **2**: 1110 (Dec. 16) 1933. (*b*) Friedemann, Ulrich: The Pathogenic Agent in Normal Human Bone Marrow: Its Nature and Relationship to the Lymphadenoma Agent of Gordon, ibid. **1**: 517 (March 24) 1934.

8. Jochmann, G., and Lockemann, G.: Darstellung und Eigenschaften des proteolytischen Leukocytenferments, Beitr. z. chem. Physiol. u. Path. **11**: 449, 1908.

9. Gordon, M. H.: Pathology and Treatment of Lymphadenoma, Brit. M. J. **1**: 635 (April 7) 1934.

10. MacKenzie, Ian, and Van Rooyen, C. E.: Relationship of Jochmann's and Other Enzymes to the Encephalitogenic Agent in Lymphadenomatous Lymphatic Glands, Brit. M. J. **1**: 406 (March 2) 1935.

autopsy were dissected as free as possible from fat and fibrous tissue, and a slice was removed for histologic examination. The remainder was weighed, minced with scissors, ground in a mortar and made into a 10 per cent suspension by the addition of beef infusion broth at a p_H of 7.2. The emulsions in cotton-stoppered test tubes were immediately cultured and then placed in a refrigerator for at least one week and often for two weeks or longer. If the cultures showed growth the emulsions were sterilized with phenol in concentrations as high as 0.5 per cent. When the glandular material was adequate a portion was ground, rapidly dried in a desiccator, transferred to a glass tube, sealed and stored in the refrigerator. After being autolyzed in the refrigerator the original emulsions were centrifuged, and 0.4 cc. of the clear supernatant fluid was injected into the occipital lobe of the brains of rabbits and a similar amount given intravenously through an ear vessel. The animals were observed daily for neurologic manifestations and records kept as to weight and temperature for at least thirty days and often for several months. Occasionally there were immediate paralysis and convulsions after the injection, but the animals so affected were not included in this series unless they appeared entirely normal within a few hours. In positive tests the animals had the rigidity, ataxia and paralysis described by Gordon after an incubation period of from three to fourteen days.

RESULTS

Lymph nodes from fifty patients were tested, some 200 rabbits being used. The nodes were obtained from thirty-seven by biopsy and from thirteen at autopsy. Many of the patients presented some clinical symptoms compatible with the diagnosis of Hodgkin's disease, and all had lymphadenopathy. In thirteen cases the diagnosis of Hodgkin's disease was made by histologic examination, while in the remainder it was based on a variety of pathologic conditions, as listed in the accompanying table, and the latter cases served as controls. The Gordon test was positive in ten of the thirteen cases of Hodgkin's disease (77 per cent) and was negative in three cases. The test was negative in thirty-five of the thirty-seven control cases (95 per cent).

The two control cases in which the Gordon test was positive are worthy of comment:

CASE 1.—A youth aged 18 had mild fever, a palpable spleen, generalized mild lymphadenopathy, clubbed fingers and bilateral bronchiectasis, with copious sputum containing Streptococcus viridans (alpha) and a partially hemolytic streptococcus (alpha prime). There were moderate secondary anemia and a leukocyte count of 10,000, with 43 per cent eosinophils. Careful investigation failed to reveal a satisfactory explanation for the eosinophilia. An inguinal and an epitrochlear lymph node were removed for histologic examination and the Gordon test. Both nodes yielded pure cultures of Streptococcus viridans. The sections showed chronic hyperplastic lymphadenitis with numerous eosinophils. The Gordon tests were positive. The status of the patient was followed for sixteen months, at the end of which he felt well and had gained considerable weight. The spleen was not palpable, and the superficial lymph nodes were smaller. He raised considerable sputum.

CASE 2.—A man aged 42, who felt perfectly well except for "swellings" on both sides of his neck, was seen at physical examination to be entirely normal except for a chain of hard discrete nodules on both sides of the neck, extending from behind the ears to the supraclavicular regions, and similar nodes in the left axilla and groin. The leukocyte count was 10,300, with 72 per cent polymorphonuclears and 2 per cent eosinophils. Biopsy of a cervical node revealed that a large portion of the lymphoid tissue was replaced by a squamous type of epithelium with active mitosis. The remaining lymphoid structure was normal except for myriads of eosinophils. A careful clinical and roentgenologic search revealed no primary source for this carcinoma. Gordon tests were positive on the third day in the two rabbits inoculated. Subsequently an axillary node was removed; it was largely replaced by epithelial growth but contained only occasional eosinophils. Unfortunately this biopsy specimen came to me in solution of formaldehyde and a Gordon test could not be performed.

Under roentgen therapy the glands in the various areas receded. The patient was seen at frequent intervals, but it was not until eleven months later that a tumor was demonstrated in the nasopharynx. This region had been examined carefully several times previously. A biopsy of the nasopharynx gave a diagnosis of lympho-epithelioma. This was undoubtedly the primary tumor. A course of supervoltage roentgen therapy caused disappearance of the nasopharyngeal tumor. When the patient was last seen, four months later, there were no evidences of recurrence and he appeared well.

These two positive tests in cases which as far as we could determine were not of Hodgkin's disease caused us to review critically the forty cases in which tests had been made. At that time eight cases of Hodgkin's disease had been studied, and in all but one the Gordon tests had been positive. There were thirty-two controls, and in all except the two cases reported the tests were negative. In an attempt to correlate the histologic structure of the lymph nodes with the response in the rabbits it became evident that the emulsions giving a positive reaction were from nodes rich in eosinophils regardless of the other histologic changes. In order to test the significance of this observation several experiments were performed with suspensions of other human tissues handled in a comparable manner.

Extracts of a cutaneous tumor from a patient with typical mycosis fungoides and from the renal cortex of a patient with subacute glomerular nephritis, both containing numerous eosinophils, gave positive Gordon reactions. Friedemann [7b] reported that normal human kidney did not elicit this reaction. It may be proposed that this observation indicates the close identity of mycosis fungoides and Hodgkin's disease, but I do not think that it necessarily does.

Rabbit tests were positive after injection of extracts of leukocytic cream separated from the blood of two patients with trichinosis, one with a blood count of 11,000 leukocytes, 31 per cent eosinophils, and the other with a count of 14,200, 54 per cent eosinophils. I have not experimented further with leukocytic creams, but others [2n] have found that any suspension of human leukocytes containing as many as "2,000 eosinophils per cubic millimeter produced a paralysis indistinguishable from that seen in the positive Gordon test, while the numbers of any other type of white blood cell appeared to exert no such influence."

I was curious as to the effects that might be produced by injection of another type of eosinophilic cell, such as that found in the hypophysis. Extracts of the anterior lobe of the hypophysis from a person who had died of an abscess of the lung and empyema and from a patient who had died of bronchopneumonia both gave negative reactions in animals.

During this period nodes from ten more patients with lymphadenopathy were tested, bringing the number of cases to the fifty reported. A study of all the microscopic slides showed remarkable agreement of positive Gordon tests and nodes generously infiltrated with eosinophils. Sections of the nodes from the three patients said by clinicians and pathologists to have Hodgkin's disease but with negative Gordon reactions

revealed exceedingly rare eosinophils. One of these patients died three months after the tests were made and another within a year, and the third is following the usual failing course of Hodgkin's disease.

Eosinophils were remarkably few in number or absent from the sections from the thirty-five control patients giving negative Gordon reactions. Three controls had nodes which histologic examination showed to be tuberculous. When suspensions of these nodes were injected into rabbits, two gave a negative reaction but the third rabbit grew loath to move, showed signs of meningeal irritation, lost weight and died in two and a half months. It did not exhibit the typical sequence of events of a positive Gordon reaction. An autopsy revealed caseous tuberculous lesions in the lungs containing many acid-fast bacilli. There was mild nonspecific lymphocytic infiltration of the meninges, but a definitely tuberculous lesion was not demonstrated in the brain. Bacteriologic examination of the original lymph node had shown acid-fast bacilli and Streptococcus viridans. The latter had been destroyed by phenol, and it was hoped that the tubercle bacilli were also destroyed, but apparently they were not. Since Munson [2g] reported positive Gordon tests with nodes from two patients with tuberculosis, I wonder whether his rabbits showed tuberculous lesions of the central nervous system which could possibly have accounted for their neurologic signs or whether there were many eosinophils present in the nodes.

The papers of Gordon and Van Rooyen should be consulted regarding the properties of the pathogenic agent present in emulsions of glands from patients with Hodgkin's disease. I add a few personal observations on the nature of this agent in verification of some of their work.

An autopsy furnished a large amount of typical Hodgkin's lymph glands heavily infiltrated with eosinophils. The patient had received all the roentgen therapy that could be tolerated with safety. Extracts of the lymph glands elicited positive Gordon reactions in three days, with death of the animals in from five to twenty days. One extract was sterilized by long centrifugation, another with phenol and a third by passage through a Seitz filter according to the technic of Van Rooyen.[2b] All rabbits gave positive reactions on the third day after inoculation. Sixty days later a portion of desiccated gland was made into a 1 to 50 suspension in broth at a p_H of 7.2. One part of the extract was frozen in a test tube in carbon dioxide at — 57 C. for ten minutes and then thawed; a second part was exposed in an open vessel to 10,000 roentgens, equivalent to approximately 20 skin doses, and a third part was untreated. All produced positive reactions in rabbits on the third day. It is apparent that roentgen therapy of the living tissue and of the extracted tissue does not inactivate the agent responsible for the reaction in rabbits. Twenty-four months later this desiccated material was still capable of producing a typical Gordon reaction in rabbits when given intracerebrally and intravenously or intracerebrally only. Brains and spinal cords from animals paralyzed by extracts from this patient and from others uniformly failed to produce the Gordon reaction when inoculated into other rabbits either immediately or after extraction.

Kelser and King [5] made careful histologic studies of the brains of guinea pigs and rabbits exhibiting the paralytic syndrome after inoculation with extracts of human and monkey bone marrow. They described reactions occurring locally at the site of injection and also more general widespread effects. The local reaction was similar to that resulting from the introduction of any destructive agent but more severe than that expected from the small amount of material injected. There were central necrosis, hemorrhage and large numbers of Gitter cells, with a peripheral zone of cytologic degeneration, vascular proliferation, perivascular glial infiltration and a mononuclear type of mild meningeal inflammation. The remote reactions were most strikingly seen in the cerebellum, where there was severe and widespread injury to the Purkinje cells. One observes a similar condition in the brains of rabbits exhibiting paralysis after inoculation with extracts of lymph nodes from patients with Hodgkin's disease. Although this phase of the problem will be more carefully detailed at a later date, I reproduce at this time examples of the lesions found. Figure 1 illustrates a field from the inoculation area in the cerebral cortex of a paralyzed rabbit. There are central necrosis, a few Gitter cells, an increase in microglia and a slight

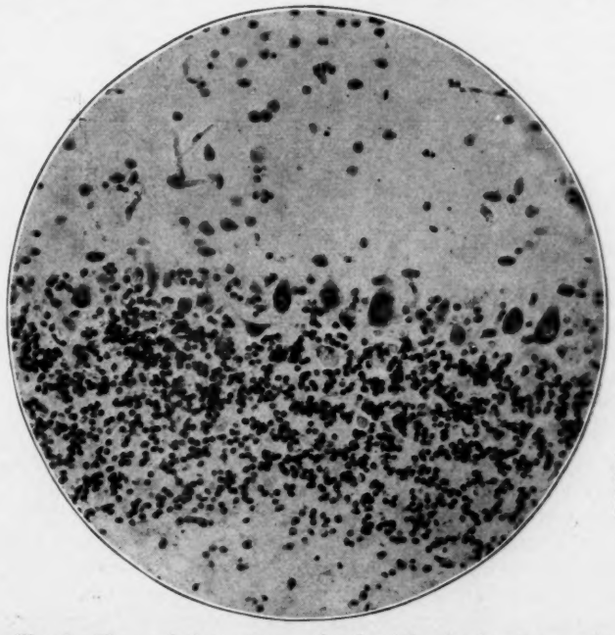


Fig. 2.—The cerebellum of a paralyzed rabbit, showing degenerative changes in the Purkinje cells (slightly reduced from a photomicrograph with a magnification of 160 diameters).

increase in perivascular glial cells. Figure 2 shows part of a folium of the cerebellum of a paralyzed rabbit, with various degenerative changes in the Purkinje cells. These cells are swollen and vacuolated and exhibit neurophagia. Several are pale staining or are mere shadows, while others have completely disappeared. There are fields in the same specimen in which no Purkinje cells can be found.

Kelser and King said that the symptoms of the affected animals are the result of a widespread functional involvement of the nervous system, caused by a chemical or enzymatic agent apparently of leukocytic origin and not by a virus.

COMMENT

The data presented is in confirmation of the conclusions of Turner, Jackson and Parker [2n] and indicate the close etiologic relation of the eosinophil to the Gordon and Friedemann phenomena. Other writers have published evidence in support of this relation but have attached no significance to their observations.

Wurm [2m] reported nine cases of clinical and histologic Hodgkin's disease in which the Gordon tests were negative and noted that the sections were singularly free of eosinophils. Van Rooyen [5] reported a positive Gordon test with material from a boy who clinically had Hodgkin's disease but histologically displayed only marked eosinophilia, with no other features sufficiently characteristic to warrant such a diagnosis. Our compilation of 192 cases of Hodgkin's disease shows that the Gordon test was positive with approximately 70 per cent of the lymph nodes. This is in complete agreement with the critical histologic studies of Pullinger [11] on the lymph nodes from thirty-nine patients with Hodgkin's disease, in which eosinophils were found in 71 per cent of the nodes.

Results with the Gordon Test

Type of Material	Histologic Diagnosis	Number of Cases	Gordon Test	
			Positive	Negative
Lymph nodes	Hodgkin's disease	13	10	3
	Lymphadenitis	11	1	10
	Leukemia, lymphatic	7	0	7
	Leukemia, myeloid	2	0	2
	Leukemia, monocytic	2	0	2
	Pseudoleukemia	1	0	1
	Lymphosarcoma	6	0	6
	Tuberculosis	3	0	3
	Carcinoma	3	1	2
	Reticulum cell sarcoma	1	0	1
	Endothelioma	1	0	1
Total		50	12	38
Skin nodule	Mycosis fungoides	1	1	0
Kidney	Subacute nephritis	1	1	0
Leukocytic cream	Trichinosis	2	2	0
Hypophysis		2	0	2

It follows that the Gordon test is of little or no value in the practical diagnosis of Hodgkin's disease. It is true that the test is positive with 70 per cent of the lymph nodes from patients with the disease and negative with 98 per cent of other lymph nodes, but this apparently is due only to the eosinophils present and undoubtedly has nothing to do with the disease itself.

The exact nature of the pathogenic agent still remains unknown. It apparently is not a virus or living agent. I favor the theory that it is a chemical or enzymatic agent.[5] It has been suggested that it may be similar to the Charcot-Leyden crystals, which are looked on as a derivative of the primate eosinophil.[2n] Future studies may be enlightening as to this agent and as to the eosinophil itself.

SUMMARY

1. In my series the Gordon test was positive in ten of thirteen cases of Hodgkin's disease (77 per cent) and negative in thirty-five of thirty-seven control cases of various lymphadenopathies (95 per cent). These cases being included, the Gordon test has been reported positive in 70 per cent of 192 cases of Hodgkin's disease and negative in 98 per cent of 251 control cases.

2. Histologic sections of the lymph nodes eliciting the positive reactions showed numerous eosinophils, while the nodes associated with the negative reactions contained very few or no eosinophils.

3. Extracts of human tissues and leukocytes which were from patients who definitely did not have Hodgkin's disease but which contained many eosinophils caused reactions in rabbits indistinguishable from those caused by the lymph nodes from patients with typical Hodgkin's disease. This supports the theory that Gordon's agent and Friedemann's agent are identical and are apparently derived from the eosinophil.

4. Histologic studies have already shown that eosinophils are easily demonstrable in the glands of some 70 per cent of patients with Hodgkin's disease, and it is in the same percentage of cases that the Gordon test is positive. Apparently it is positive only by virtue of these cells.

5. The Gordon test is of no more practical value in the diagnosis of Hodgkin's disease than is the finding of eosinophils in the lymph nodes.

11. Pullinger, B. D.: Rose Research on Lymphadenoma: Histology and Histogenesis, Bristol, England, John Wright & Sons, Ltd., 1932.

ABSTRACT OF DISCUSSION

DR. F. H. LAMB, Davenport, Iowa: I should like to ask Dr. McNaught what percentage of the cases in which the lymph nodes were tested were from living patients, and how that percentage compares with those from the dead.

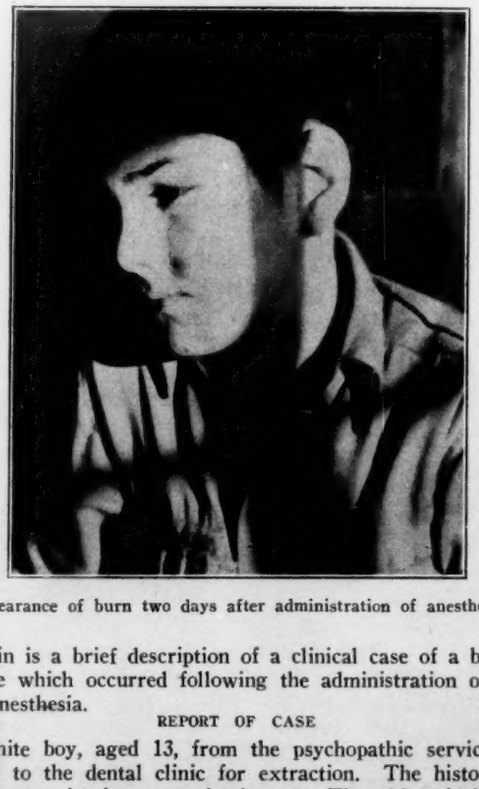
DR. JAMES B. MCNAUGHT, San Francisco: Lymph nodes from two of the thirteen cases of Hodgkin's disease submitted to the Gordon biologic test were obtained at autopsy. Both gave positive tests. The other eleven specimens were biopsies. Eight of these were positive and three were negative. Other than the simple tests, most of the experimental work was performed on autopsy material, which obviously was available in larger quantities.

Clinical Notes, Suggestions and New Instruments

VINETHENE BURN

SYDNEY S. LYONS, D.D.S., M.D., NEW YORK

Vinethene, since its introduction to clinical anesthesia in 1931, has been the subject of numerous reports. A review of these articles failed to reveal any reference to the possibility of this agent producing a skin burn.



Appearance of burn two days after administration of anesthetic.

Herein is a brief description of a clinical case of a burn on the face which occurred following the administration of vinethene anesthesia.

REPORT OF CASE

A white boy, aged 13, from the psychopathic service, was brought to the dental clinic for extraction. The history and physical examination were irrelevant. The skin of the face was apparently normal. The patient was anesthetized in a dental chair. Vinethene was administered by an open drop

From the Division of Anesthesia, Bellevue Hospital.

technic. This method consisted in cupping a regulation 4 by 4 inch hospital gauze square (40/44 mesh, six thicknesses) over the nose and mouth to form an evaporating surface. Vinethene was then dropped on the gauze from freshly opened original 25 cc. containers until surgical anesthesia was obtained. Less than one minute after induction was begun the gauze was rearranged, permitting the surgeon access to the mouth. Extraction required twenty-one minutes, during which time vinethene was constantly dropped on the gauze held in place by the anesthetist's thumb and finger. After completion of the operating procedure the gauze was removed. A total of 46 cc. of anesthetic agent had been used. Recovery from anesthesia was complete in less than two minutes and the patient soon walked to the ward, accompanied by an attendant. On his arrival he complained of a sore cheek. Some six hours later, a vesicle was noted and examination the following day revealed a superficial lesion lateral to the left ala nasi, which was evidently a burn. The site of the cauterized area corresponded to the position over which the anesthetist placed his thumb to hold the gauze. Its configuration resembled the part of the thumb which had kept contact between the gauze and the face. The burn was treated with boric acid ointment and healing was complete in seven days. A photograph taken on the second day after anesthesia is reproduced.

This case illustrates that vinethene may cauterize the skin as does ether, when it is confined to an area from which it cannot evaporate easily. If pressure is applied to the area it may enhance the possibility of a burn. It is advised that with technics similar to that used in the case reviewed, the skin be protected by applying a bland ointment before administering anesthesia.

Twenty-Sixth Street and First Avenue.

A MICROSCOPIC PRECIPITIN TEST FOR TYPING PNEUMOCOCCI

ISABELLE G. SCHAUB, A.B., AND ROGER D. REID, PH.D., BALTIMORE

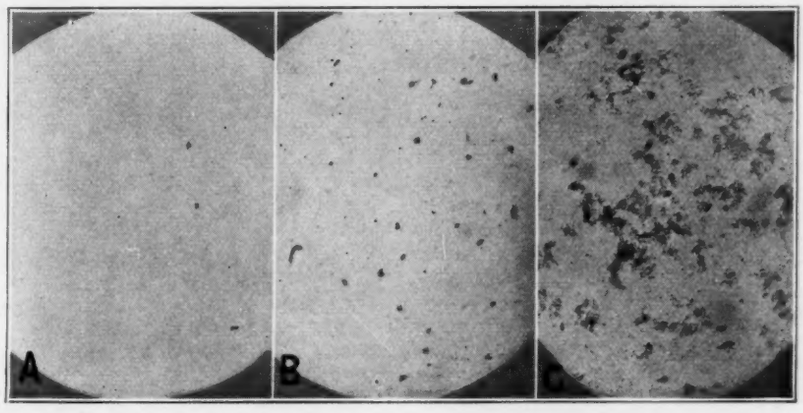
The rapid typing of pneumococci is becoming increasingly important with the development of therapeutic serums for the various types. The Neufeld method is admirably suited when the organisms are present in sputum, but difficulties are encountered when typing is attempted from cultures. The macroscopic agglutination of cultures requires the use of pipets and test tubes, and the quantity of serum required represents considerable expense. We have employed a microscopic precipitin technic by which the pneumococci can be typed from cultures quickly and with a very small amount of immune serum. The technic proposed by Brown [1] for grouping the hemolytic streptococci has been adapted for this purpose.

PREPARATION OF THE ANTIGEN

Cultures of pneumococci from blood, spinal fluid or other sources taken during life or at autopsy may be grown in meat infusion broth containing a few drops of serum or ascitic fluid [2] incubated at 37 C. for from six to eighteen hours. The culture is lysed by the addition of two drops of a 10 per cent aqueous solution of sodium desoxycholate (containing 1 : 50,000 merthiolate to prevent the growth of molds) per cubic centimeter of culture.[3] In from fifteen to thirty minutes the organisms are dissolved, and tests have shown that the lysate is sterile. The antigen is now ready for use. In some instances an excess of sodium desoxycholate in the presence of serum will cause the culture medium to gel. This may be liquefied by warming slightly without decreasing the efficiency of the test.

PREPARATION OF THE TYPING SERUM

For making this test, horse antipneumococcus serum such as is used for macroscopic agglutination tests, diluted 1 : 10 in physiologic solution of sodium chloride, is used. Such dilutions have been found satisfactory after refrigeration for as long as six weeks.



A, negative precipitin reaction; *B*, doubtful cross reaction; *C*, typical positive reaction.

Rabbit antipneumococcus serum as prepared for the "quellung" test, diluted 1 : 1 in salt solution, has been used, but the reaction takes place more slowly, sometimes requiring from one to two hours for marked precipitation to take place. The reaction with the diluted horse serum takes place rapidly, and readings can be made after from fifteen to thirty minutes. By adding 1 per cent aqueous methylene blue to the horse serum the reading of results is facilitated, although the dye is not essential to the test. Dye is already present in the rabbit "quellung" serum.

Attempts were made to place the organisms into groups by means of commercially prepared "quellung" grouping serums or by mixing the typing serums prepared from horses in proportions based on the titer of the species antiserum, but results obtained were not sufficiently uniform to be considered satisfactory.

TECHNIC OF THE TEST

The Petri dish-hanging drop technic described by Brown is used for making the test. A disk of moist filter paper is placed in the lid of the dish. The bottom of the dish is ruled on the bottom surface with a wax or diamond pencil, providing sixteen 12 mm. squares. In the performance of the test two Petri dishes are required for each organism to be typed. In one dish the antigen is set up against each of the fifteen types of antiserum (diluted), the sixteenth square being used for an antigen-salt control. In the second dish the remaining type antiserums are set up. It has been found most practicable to add one platinum loopful of the antigen to each of five squares and mix with them an equal amount of the appropriate typing serums, and then to proceed with the next five squares in the same manner. This prevents drying of the loop of antigen before it is possible to add the antiserum, as is likely to happen if the antigen is placed in all fifteen squares before the antiserums are added. A 2 mm. loop of platinum rather than one of the platinum substitutes is recommended. The loop should be thoroughly flamed and cooled each time before being introduced into the serum.

READING OF RESULTS

The mixtures of serum and antigen are held from fifteen to thirty minutes and readings are made with the 16 mm. objective of the microscope, the light from the condenser being

From the Department of Pathology and Bacteriology, Johns Hopkins University.

The Division of Laboratories and Research, New York State Department of Health, the Bureau of Laboratories, New York City Department of Health, the Bureau of Bacteriology, Maryland State Department of Health, and Sharp and Dohme, Philadelphia, supplied the cultures and antiserums for this investigation.

1. Brown, J. H.: A Simplified Method for Grouping Hemolytic Streptococci by the Precipitin Reaction, J. A. M. A. **111:** 310 (July 23) 1938.

2. Other mediums such as meat infusion broth with or without blood may be used. A small amount of dextrose may be added to stimulate growth, but in this case it is necessary to adjust the reaction of the medium by the addition of sodium hydroxide until the indicator, bromthymol blue, is bluish green, indicating that the solution is slightly alkaline before the sodium desoxycholate is added. The cultures may also be grown on infusion agar slants containing 10 per cent rabbit blood and the organisms washed off with sterile saline solution and lysed. A satisfactory antigen has also been prepared by using the peritoneal washings from a mouse previously injected with infected material such as sputum.

3. This method for the preparation of the antigen does not actually introduce an additional step, since solubility in sodium desoxycholate is one of the first tests to be made in the identification of pneumococci. Leifson, Einar: The Use of Sodium Desoxycholate for the Identification of Pneumococci, J. A. M. A. **104:** 213 (Jan. 19) 1935.

allowed to pass through the moist filter paper. Gentle rotation of the plates hastens the formation of large clumps of precipitate. The appearance of large clumps of precipitate (*C* in the illustration) indicates a positive reaction. Negative results are indicated by the absence of such clumping (*A*). Doubtful or questionable results are seldom encountered but can be eliminated by comparison with the control and a known positive. In using this technic for the first few times it is suggested that known positives and negatives be set up as controls to familiarize the worker with typical reactions.

Infrequently, though occasionally, cross reactions occur. These may be distinguished from typical positive reactions with a little experience. Such a doubtful cross reaction is shown in *B*.

There appears to be no advantage in incubation or refrigeration of the mixtures.

RESULTS

We have made repeated tests on cultures belonging to all the known types of pneumococci, including the Cooper strains. We have also identified and made repeated tests on fifty-five cultures taken from infections and at autopsies. Unknown cultures have been checked by other methods and complete agreement was found in every instance.

With the method described, cultures of pneumococci may be typed in a much shorter time than with the macroscopic test; more reliably, in our opinion, than with the "quellung" test; at a minimum expense for serum and antigen, and with the advantage of working with a sterile antigen.

1833 East Monument Street.

Special Clinical Article

HODGKIN'S DISEASE

SIXTY CASES IN WHICH THERE WERE INTRATHORACIC LESIONS

CLINICAL LECTURE AT SAN FRANCISCO SESSION

C. B. WRIGHT, M.D.

MINNEAPOLIS

In 1832 Hodgkin reported seven cases of unusual glandular swellings. His description was clinical. In 1865 Samuel Wilks reported thirteen similar cases and named the condition "Hodgkin's disease." In 1926 Herbert Fox [1] reexamined Hodgkin's pathologic specimens and found that of the seven cases three were of Hodgkin's disease, one was of syphilis, one was of tuberculosis and one was probably of lymphatic aleukemia. For the next seventy years tuberculosis followed Hodgkin's disease like a shadow. It is difficult to realize today what a common condition glandular tuberculosis was previous to modern food sanitation and the tuberculin testing of cattle. In 1902 Dorothy Reed definitely differentiated Hodgkin's disease from tuberculosis. The two diseases are still occasionally found associated. It is very interesting to compare this condition with that in our series. Four patients had calcified nodes, one had active tuberculosis and Hodgkin's disease in the same mediastinal gland and one had terminal tuberculous pericarditis.

Since 1902 pathologists have added much confusion to the literature with a great variety of names for this disease. Wallhauser [2] found fifty different names for Hodgkin's disease in 1933.

There is no doubt that biopsy is the most exact method of diagnosis of this disease in the living. This presupposes that the specimen furnishes the pathologist with tissue containing the typical lesions. Therefore it should be taken from a characteristic gland. It should be taken, of course, under the most careful antiseptic conditions, as there is nothing more difficult to deal with than the complication of an infected sinus. When Dorothy Reed cells are present they are pathognomonic. In many slides there are large reticulum cells either singly or in groups, not one of which, however, is a typical Dorothy Reed giant cell. According to Bell [3] the increase in the number and size of the reticulum cells is the most constant feature of the disease. Fibrosis is usually present and is usually regarded as indicating an advanced stage, but it may be found early in the disease. In some cases fibrosis is prominent in both large and small lymph nodes; in others it is inconspicuous. The cellular forms of Hodgkin's disease blend with leukemia, and in rare cases one finds a leukemic blood picture with typical Hodgkin's disease in the lymph nodes. There is a similar blending with lymphosarcoma and leukemic reticulo-endotheliosis.

I have reviewed sixty cases of Hodgkin's disease, in all of which, during the period of observation, there were intrathoracic complications; all had been observed long enough so that there was a fairly good clinical history and a physical examination had been made. All the patients had roentgen treatment and were under observation for a considerable period.

Figure 1 shows the first indications of the disease as recorded in the chart from the physical examination or in the history taken from the patient or reported by the referring physician.

The patients did not all have intrathoracic lesions on first examination. Some had them then and the rest acquired them later, while they were under observation; many had complications in other parts of the body. In addition to the more common conditions shown in figure 1, there was a variety of unusual conditions.

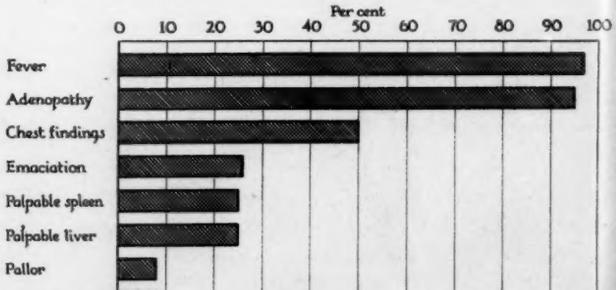


Fig. 1.—First indications of Hodgkin's disease in sixty cases.

In two cases there was jaundice. In one case it was present for about two weeks and then cleared up. In the second case there was a history, on admission, of jaundice coming on about a week after removal of the gallbladder for chronic cholecystitis and cholelithiasis. Glands were later found in the neck which on biopsy proved to be typical of Hodgkin's disease. There were two fatal cases of intestinal perforation due to Hodgkin's disease. There was one case of involvement of the spinal cord with paralysis. There

Read in the Medical Division of the General Scientific Meetings at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 14, 1938.

1. Fox, Herbert: Remarks on Microscopical Preparations Made from Some of the Original Tissue Described by Thomas Hodgkin, 1832, Guy's Hosp. Rep. **86**: 11 (Jan.-April) 1936.

2. Wallhauser, Andrew: Hodgkin's Disease, Arch. Path. **16**: 522-562 (Oct.), 672-712 (Nov.) 1933.

3. Bell, E. T.: Textbook of Pathology, Philadelphia, Lea & Febiger, 1938.

was one case of extensive involvement of bone and one case of involvement of the skin.

In one case the disease simulated nontropical sprue:

CASE 1.—A woman aged 63 began in 1932 to have diarrhea, generalized weakness and shortness of breath on exertion, and she lost 50 pounds (23 Kg.) in weight. In the fall of 1935 pain in the upper part of the abdomen developed. The liver and spleen became palpable; she had marked secondary anemia, and the white blood cell count was low. The skin was leathery, with a light diffuse pigmentation. No gastrointestinal lesions were found by x-ray study, and a diagnosis of cancer of the liver was suggested. However, with a generous diet and liver the patient gained 20 pounds (9 Kg.) and felt well. Her blood count rose to normal. One year later the diarrhea returned. Three months later vomiting, partial paralysis of the legs, weakness of the hands and slow scanning speech developed. Vibration and the tactile senses were normal. All serologic tests were negative except that for the bacillus of Flexner. The patient had some soreness of the mouth and secondary anemia. No eosinophilia was noted in any of her blood examinations. At times she had a fever, and in her final illness her temperature was as high as 103 F. No superficial glandular enlargements were noted at any time. A clinical diagnosis of nontropical sprue was suggested. The patient died five years after her first symptoms. Postmortem examination showed Hodgkin's disease of the mediastinal nodes, marked Hodgkin's disease of the spleen, tuberculous pericarditis, hyperplasia of the bone marrow, fatty liver with necrosis, chronic benign ulceration of the rectum and pigmentation of the skin. At no time had she any definite symptoms referable to the chest. The brain and cord were not examined at autopsy.

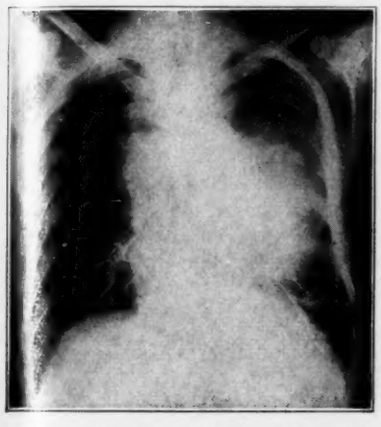


Fig. 2 (case 3).—Invasion of the left lung and very large mediastinal glands.

Itching is common in Hodgkin's disease and occurs without lesions other than excoriations:

CASE 2.—A woman aged 41, who complained for eight months of intense itching of the skin, had been treated without improvement. On examination she was found to have enlarged glands in the left supraclavicular region, and biopsy showed typical Hodgkin's disease. X-ray examination showed enlarged glands in the mediastinum. The itching grew less with high voltage roentgen therapy, and the glands disappeared.

Desjardins [4] expressed the opinion that pruritus and cutaneous lesions could be cured by irradiation over the liver. Roentgen therapy does not always relieve the itching. Kasaback and McAlpin [5] relieved two of five patients with roentgen treatment over the liver.

Certain clinical and laboratory observations have been used as criteria for the diagnosis of Hodgkin's disease. Discrete, painless and slowly developing enlargement of the peripheral glands is the most common clinical characteristic. Practically all patients have fever.

LABORATORY STUDY

In only eleven of the sixty cases was there eosinophilia. The degree varied from time to time during the observation. The highest percentage of eosinophils in any case was 24, and in many of the cases no eosinophils were found in the circulating blood. Secondary anemia is a fairly constant sign in the cases of very active involvement. However, in many cases in which the condition seemed severe the blood counts were within normal limits or showed only a slight degree of anemia. The anemia seemed to have no relationship to roentgen treatment; in fact, many of the patients showed improvement in their blood after this procedure. Leukocytosis was a not uncommon manifestation; white blood cell counts as high as 20,000 or 30,000 were recorded. Leukopenia was found not infrequently; the lowest count recorded was 2,300. The degree of leukopenia varied in individual patients. There was no uniformity in any of the blood counts, as they varied with the same patient at different times and with different patients.

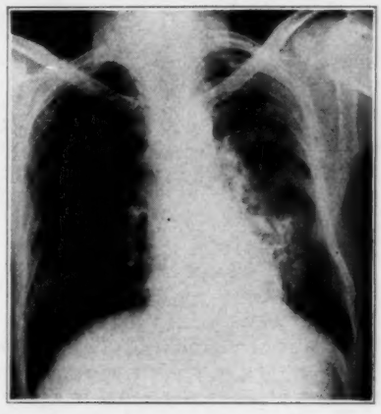


Fig. 3 (case 3).—Results of treatment.

In cases in which tissue is not accessible for biopsy a specific test of some kind would be most desirable. Gordon [6] devised a test which he thought was specific for Hodgkin's disease. It consisted of inoculating broth suspensions of Hodgkin's tissue into the brain of rabbits or guinea pigs, producing a characteristic paralysis. His work was verified by other observers. Friedman showed, however, that the same type of paralysis of the same kind of animals could be produced with extracts of bone marrow, spleen or glands. Turner and Jackson [7] concluded that this test is positive because of the presence of eosinophils and that it would be negative when eosinophils were absent. In the present series three patients were tested by this method, and the results with two were positive.

Fig. 4 (case 6).—Extensive involvement of the left ilium.

Fifty-four patients had superficial glandular enlargements, and biopsies were performed during their period of observation. Five patients had biopsies or were examined post mortem elsewhere. One patient had no

4. Desjardins, A. U.: Radiotherapy for Hodgkin's Disease and Lymphosarcoma, J. A. M. A. **99**: 1231-1236 (Oct. 8) 1932.

5. Kasaback, H. H., and McAlpin, Kenneth R.: Mediastinal Hodgkin's Disease, New York State J. Med. **38**: 171 (Feb. 1) 1938.

6. Gordon, M. H.: Remarks on Hodgkin's Disease, a Pathogenic Agent in the Glands, and Its Application in Diagnosis, Brit. M. J. **1**: 641-647 (April 15) 1933.

7. Turner, Joseph C., and Jackson, Henry, Jr.: The Etiological Relationship of the Eosinophil to the Gordon Test for Hodgkin's Disease, J. Clin. Investigation **16**: 657 (July) 1937.

superficial glands showing at any time and therefore no biopsy. In one case the biopsy did not show Hodgkin's disease but autopsy did.

INTRATHORACIC LESIONS

The intrathoracic lesions are of four varieties: (1) enlargement of the mediastinal glands, (2) involvement of the pulmonary parenchyma, (3) involvement of the pleura and (4) combinations of these regional types.

In fifty-seven cases enlarged mediastinal glands were demonstrated by roentgenogram. Twenty-one patients had parenchymal involvement, and eighteen of these had also enlarged mediastinal glands. Three of these patients had parenchymal lesions only. Seventeen patients had pleural effusion; all of these had mediastinal enlargements. Seven had pleural effusion and involvement of the mediastinal glands.

REPORT OF ADDITIONAL CASES

CASE 3.—A man aged 49, who began to have symptoms in 1932 in the form of influenza of the stomach with productive cough, was admitted to the hospital May 8, 1934. It was discovered that he had a tumor which at first was thought to be a bronchiogenic carcinoma. Biopsy of material from a bronchus, however, resulted in a diagnosis of subepithelial fibrosis. Biopsy of an enlarged lymph gland in the axilla showed only hyperplasia. A roentgenogram (fig. 2) showed invasion of the left lung and very large mediastinal glands. The growth responded so remarkably to roentgen treatment (fig. 3) that the diagnosis was changed to lymphosarcoma and later to Hodgkin's disease. The patient was discharged June 2, 1934, and died September 9. No autopsy was performed.

CASE 4.—A girl aged 11, whose first symptoms appeared in October 1930 in the form of swollen glands, began to cough in November 1930. She was admitted to Glen Lake Sanatorium, Oak Terrace, Minn., April 24, 1931, when biopsy resulted in a diagnosis of Hodgkin's disease. The glands enlarged were the left cervical and later the left axillary. Examination of the chest revealed decreased tactile fremitus, dulness and diminished breath sounds over the left portion. The tumor responded very well to roentgen treatment, but the patient died June 24, 1932. No autopsy was performed.

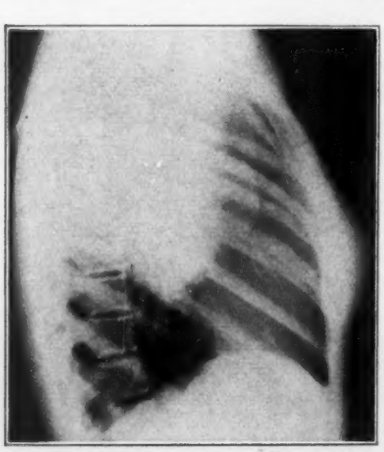


Fig. 5 (case 7).—Extensive tumor.

CASE 5.—A woman aged 40 had her first symptoms in 1935, when lumps appeared in both breasts and under the left ear. She lost 10 pounds (4 Kg.) in weight. The diagnosis, made by biopsy Nov. 11, 1937, at the University of Minnesota, was Hodgkin's disease. Glands were enlarged under the left ear and both breasts, the medial angle of the left scapula and the lateral aspect of the left calf. The chest was clear on physical examination. The patient died November 13, two days after biopsy. No autopsy was performed.

CASE 6.—A man aged 36, who began to have symptoms in September 1933 with pain in the left hip, had experienced marked itching of the skin since 1937. The diagnosis, made by biopsy at the University of Minnesota in January 1938, was Hodgkin's disease. The glands enlarged were the supraclavicular and submaxillary and those in the groins. The thigh was swollen and the left ilium extensively involved (fig. 4). A roentgenogram of the chest showed areas of increased density in both lung fields, involvement of several ribs and of the left scapula and bilateral involvement of both lungs. The patient died Feb. 6, 1938.

CASE 7.—A girl aged 15 had her first symptom in 1936 in the form of itching, which had been diagnosed elsewhere as scabies. A diagnosis of Hodgkin's disease was made by biopsy at Ancker Hospital, St. Paul, Dec. 15, 1936. The glands enlarged were the cervical, inguinal and epitrochlear. A roentgenogram of the chest (fig. 5) showed enlarged hilar shadows on both sides and mediastinal adenopathy. The itching decreased and there was marked regression of the mediastinal masses with roentgen treatment (fig. 6). The patient was still alive March 10, 1938.

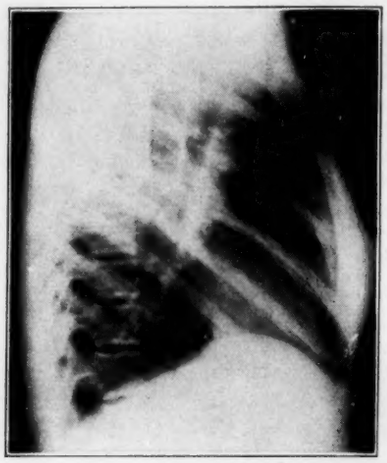


Fig. 6 (case 7).—Almost complete absence of tumor after roentgen treatment.

CASE 8.—A man aged 20, whose first symptoms, in 1924 or 1925, indicated that he had pleurisy with effusion, was well from that time to about November 1928, when he felt weak and had pain in the right axilla. A diagnosis of Hodgkin's disease was made by biopsy at the University of Minnesota Dec. 27, 1928. The supraclavicular glands were enlarged. Examination of the chest showed increased tactile fremitus, impaired resonance in the upper part of the back on both sides and rales. A roentgenogram of the chest showed a large mass in the right hilus attached to the anterior wall of the chest, posterior to the level of the trachea, and thickening of the pleura on the left side. After treatment the tumor on the right side practically disappeared. Later there was continued improvement on the right side but more evidence of parenchymal involvement at the base of the left lung. The patient died Nov. 8, 1933.

CASE 9.—A youth aged 17 had his first symptoms, consisting of pain in the left shoulder and colds, in May 1934. Swelling in the neck began in August. No biopsy was reported. The patient was admitted to the hospital November 24. The glands enlarged were the left anterior cervical and the right inguinal. Examination of the chest showed dulness over the entire left side. The lower border of the left lung could not be determined. Superficial veins over the chest were dilated. A roentgenogram of the chest showed a large mass, which looked like lymphosarcoma, involving the left side of the mediastinum and another definite area in the right lung. The patient died Dec. 24, 1934; the diagnosis at autopsy was teratoma.

CASE 10.—A man aged 52 had as his first symptom a mass in the upper part of the abdomen and dyspnea, which appeared in September 1935. A tumor was removed in January 1936 and was diagnosed as lymphosarcoma. The patient was admitted to the hospital February 19. One gland was enlarged. A roentgenogram of the chest (fig. 7) showed a suggestion of aneurysm of the descending aorta because of expansible pulsation, metastases in the right pleura and bilateral pleural effusion. When last seen, Oct. 10, 1936, the patient was not responding well to treatment; his condition was worse and the tumor was larger. Autopsy showed a Hodgkin growth completely surrounding the aorta and giving an expansile appearance.

CASE 11.—A man aged 33 had as his first symptoms, in 1928, a sharp pain in the right side of the chest and a temperature between 101 and 102 F. in the afternoon. There was recurrence with cough and effusion in the chest in April 1929. In October 1929 a tumor mass in the mediastinum was found by means of x-ray examination. No biopsy was reported. On admission to the hospital no superficial adenopathy was found. Examination of the chest showed impaired resonance and

increased fremitus over the right side. A roentgenogram showed a small amount of fluid in both sides of the chest and a large mass in the right side of the superior mediastinum, lobular and irregular. The patient was discharged from the hospital Feb. 22, 1930, and died July 10, 1931. Autopsy revealed no Hodgkin's disease, but there were active pulmonary and mediastinal node tuberculosis and amyloid disease.

CASE 12.—A man aged 54, who had as his first symptoms cough and cold, some mucoid sputum, loss of weight and a tendency to tire easily, was admitted to the hospital April 10, 1930. The Wassermann reaction was positive. Fluoroscopic examination of the chest showed a large aneurysm, not pulsating, which extended to the right and left of the mediastinum. A roentgenogram of the chest (fig. 8 *A*) showed an aneurysm of the transverse and descending portions of the arch of the aorta, possibly a double aneurysm, and displacement of the aorta. The patient was last seen Jan. 16, 1931.

CASE 13.—A man aged 21, whose first symptoms were cough, swelling of the face and neck, loss of weight, weakness and shortness of breath, which he had experienced since January 1930, was admitted to the hospital April 9, 1930. Biopsy of the glands in the neck resulted in a report of Hodgkin's disease. The patient had one terrific attack of dyspnea and cyanosis, during which he had to be put in an oxygen tent and tracheotomy was performed. He improved with roentgen therapy. Nodes were present on the right side at the angle of the jaw, there was a mass of glands in the anterior triangle of the neck and veins of the upper part of the chest were dilated. A roentgenogram of the chest (fig. 8 *B*) showed a large lobulated mass extending from the superior mediastinum into both lungs, bilateral pleural effusion and pulmonary abscess. The patient was last heard from Aug. 8, 1930.

THERAPY

Before considering the therapy of Hodgkin's disease I wish to quote from Osler's description published in 1909. He suggested the surgical removal of localized glandular swellings when they are not too large. He also recommended the use of solution of potassium arsenite. At that time x-rays were just beginning to be used and in some cases the condition had responded well. However, he concluded:

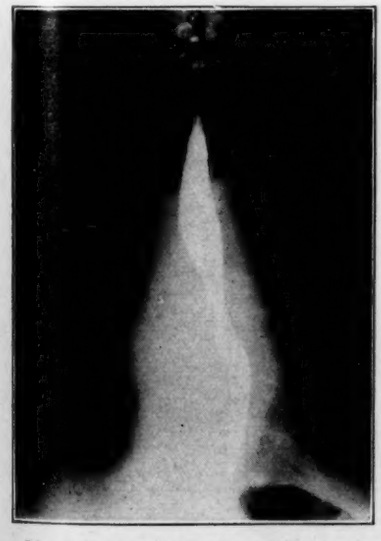


Fig. 7 (case 10).—Barium sulfate in the esophagus with relation to the growth.

> There are acute cases in which the enlargements spread rapidly and death follows in three or four months. As a rule, the disease lasts two or three years. Remarkable periods of quiescence may occur in which the glands diminish in size, the fever disappears and the general condition improves. Even a large group of glands may almost completely disappear or tumor mass on one side of the neck may subside while the inguinal glands are enlarging.

No more is known today about the cause of Hodgkin's disease than Osler knew in 1909. Until the cause is known treatment will be empiric. Surgical intervention at present is seldom used. Solution of potassium arsenite is not mentioned in modern textbooks. The only treatment considered seriously is irradiation. Reports are appearing from time to time in which the results of roentgen therapy are estimated. Kasaback and McAlpin, in a recent report on a large series of cases, emphasized diet as well as roentgen therapy. Regarding the latter one may conclude:

First, that there is general agreement that high voltage roentgen therapy is not harmful to the patient in doses sufficient to affect this disease.

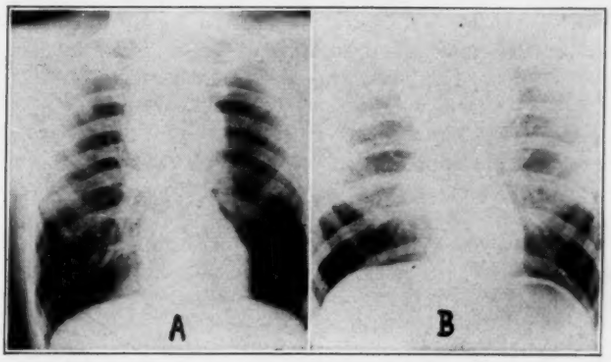


Fig. 8.—*A*, case 12, syphilis with aneurysm; *B*, case 13, mediastinal Hodgkin's disease.

Second, that the response to high voltage roentgen therapy of Hodgkin's disease, lymphosarcoma, with which it is most often confused, and to a lesser degree lymphatic aleukemia is as a rule definite and in cases in which the growths are producing pressure on vital organs may be life saving.

Third, that general irradiation of glands and bone is no longer advocated as a prophylactic measure.

Fourth, that the plan now is to treat local manifestations of the disease thoroughly as they arise.

Sensitivity of growths to treatment varies, and the development of resistance to x-rays seems likely. Some patients have this little understood resistance from the beginning; others seem to acquire it after repeated treatment, and the disease rapidly spreads.

The knowledge gathered from tumor clinics will increase, and clinicians should do all they can to assist in therapy. Patients respond well to blood transfusions when anemic, and this procedure also may be life saving. The general edema will often respond remarkably to mercurial diuretics. The diet and general hygienic surroundings should be carefully supervised. One must keep in mind the fact that this disease, which is now generally considered some form of malignant process in the reticulo-endothelial system, may, as some authorities still think, be parasitic in origin.

It is true that the condition in many cases is acute and resists all forms of treatment. The great majority of patients, however, live a considerable length of time, and a few live many years. By means of the available agencies the average period of life can probably be prolonged.

STATISTICAL SUMMARY OF RESULTS OF TREATMENT IN SIXTY CASES

Forty-five of the sixty patients observed were followed until their death. The average duration of life was forty months. Twenty-three of the patients lived over forty months; the average length of life was sixty months. Twenty-one patients lived less than forty months; the average length of life was twenty months. Two patients were lost track of and presumably died, but they are not considered.

For the thirteen patients now living, the average length of the disease is fifty months. Seven of these patients have had the disease seventy-two months. The majority are in fairly good health. Some are working, and others are in a condition of semi-invalidism.

An attempt was made to estimate the length of life after the onset of intrathoracic complications. In some cases there were in addition other complications. In the thirty-nine cases in which this estimate could be made, the average survival period was twenty-three months.

Kasabach and McAlpin found that the average survival period of thirty-eight patients adequately treated was five years and four months. Twenty patients inadequately treated survived three years and three months. In seven cases in which no treatment had been given the survival period was three years and one month.

In our series the shortest period from onset to termination was seven weeks. The patient was a woman aged 40.

The longest period was twenty-six years. In this case the diagnosis of Hodgkin's disease was made by Dr. E. T. Bell in 1910, and several biopsies subsequently confirmed the diagnosis. The patient was treated with roentgen radiation by Dr. Schons from time to time as growths appeared. On three occasions high voltage roentgen therapy apparently saved her life. At autopsy, in 1936, the lesions of Hodgkin's disease were found in the mediastinal and abdominal lymph nodes, liver, spleen and lungs. This case was not included in our statistics.

The following case illustrates the advanced stage in which patients come for treatment:

CASE 14.—A woman aged 51, with a history of easily palpable glands in the right side of the neck and right axilla for three years, when admitted to the Northwestern Hospital had general anasarca, fluid in both pleural cavities and abdomen, involvement of the mediastinal glands, enlargement of the liver and spleen, and large masses in the pelvis, which had led to the diagnosis of possible pelvic carcinoma with metastases. She had marked secondary anemia and a fever. Biopsy showed Hodgkin's disease. She was given salyrgan, blood transfusion and high voltage roentgen therapy over the chest and abdomen. She improved, the edema disappeared, the glands decreased in size, the liver and spleen became smaller and she left the hospital in fairly good health. She died a few weeks later of what appeared to be coronary occlusion. No autopsy was permitted.

Can a patient recover from Hodgkin's disease? The following case is illustrative:

CASE 15.—A man aged 59 had two operations for removal of enlarged glands in his neck. Biopsy by Dr. Bell indicated Hodgkin's disease. The glands recurred the same year and he was treated thoroughly over the neck by high voltage roentgen therapy. He is now 70, has had no subsequent treatment and has had no recurrence after eleven years.

CONCLUSIONS

Hodgkin's is a common disease. The cause is not known. The pathologic changes are well understood, and biopsy is the only sure way of making the diagnosis and should be done early and aseptically. High voltage roentgen therapy is often life saving and if used adequately will probably prolong life. Intrathoracic complications respond well to such therapy. Blood transfusions and mercurial diuretics are at times valuable. The general hygienic surroundings and diet are important.

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Special Article

VITAMIN C

METHODS OF ASSAY AND DIETARY SOURCES

OTTO A. BESSEY, PH.D.

BOSTON

This article and others recently published or to be published comprise a new series on the present status of our knowledge of the vitamins. They have been prepared under the general auspices of the Council on Pharmacy and Chemistry and the Council on Foods. The opinions expressed are those of the authors and not necessarily the opinions of either council. Reprints are not available but the articles will be published later in book form.—ED.

The isolation, synthesis and development of practical methods of assay have given a great stimulus to the study of vitamin C.[1] More papers have appeared on methods of assay and distribution for vitamin C than for all the other vitamins combined. Therefore, no attempt is made here to present a systematic review of the literature. This has been done amply in the monograph by Sherman and Smith,[2] the yearly volumes of the *Annual Review of Biochemistry*,[3] the bulletin of the United States Department of Agriculture on "Vitamin Content of Foods"[4] and numerous reviews.[5] The facts and comments presented in this review may serve to give a general idea of the present state of the subject.

BIO-ASSAY

Chemical methods have rapidly replaced vitamin C determinations by bio-assay for many types of investigations. However, the more specific animal tests continue to be necessary in order to avoid the risk of misinterpretation of the chemical tests.

Guinea pigs kept on certain purified diets fail to gain weight, and the specific pathologic changes of scurvy develop. The degree of protection or cure of the deficiency bears a quantitative relation to the amount of the vitamin administered. This principle forms the basis for biologic methods of vitamin C analyses.

Preventive Method.[6]—The technic of Sherman and his associates,[2] built on the experience of earlier investigators as well as their own studies, has continued to be the most generally used for animal assay purposes. Briefly, the method is as follows: Young guinea pigs are fed ad libitum a basal vitamin C-free diet which theoretically supplies everything necessary for their normal nutrition except vitamin C. Negative control animals are kept on the basal diet only, while other animals are fed graduated amounts of the material to be tested. After from six to ten weeks the degree of protection is estimated by a standard postmortem appraisal of the extent of hemorrhage, the beading and enlargement of the costochondral junctions, the softness of the mandibles, scapulas and ribs, and the looseness of the incisors. An amount of test material just

From Harvard Dental School and the Department of Pathology, Harvard Medical School.

1. Now named ascorbic acid or cevitamic acid.

2. Sherman, H. C., and Smith, S. L.: The Vitamins, American Chemical Society Monograph, New York, Chemical Catalog Company, Inc., 1931.

3. (*a*) Harris, L. J.: Vitamins, in Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press **1**: 357, 1932; **2**: 263, 1933; **3**: 264, 1934; **4**: 347, 1935. (*b*) von Euler, Hans: The Water Soluble Vitamins, ibid. **5**: 365, 1936. (*c*) Sherman, Caroline C., and Sherman, H. C.: The Vitamins, ibid. **6**: 346, 1937.

4. Daniel, Esther P., and Munsell, Hazel E.: Vitamin Content of Foods, Miscellaneous Circular 275, U. S. Department of Agriculture, Bureau of Home Economics, June 1937.

5. King.[23] Fellers.[48]

6. Sherman and Smith.[2] Coward.[14] Coward and Kassner.[16]

sufficient to afford complete protection from macroscopic scurvy is selected as a unit, and the results of all analyses are expressed in this unit.[7] With experience and by the use of the survival period, weight and degree of scurvy, one can estimate the degree of protection afforded by the lower test levels, thus bringing into a quantitative rating those animals which are not completely protected. The general uniformity of the test can now be improved by comparing the rate of growth and the intensity of the macroscopic lesions in the test animals with those in a similar group of animals which received graded levels of pure ascorbic acid.[8]

Curative Method.—Harris [9] and his associates have introduced a recovery method which is very useful. Less material is required and there is considerable saving in time and expense. Guinea pigs are kept on a basal diet as previously described, and after from two to three weeks animals are selected which show symptoms of scurvy and have begun to lose weight evenly. Graduated daily doses of the test material are then fed. After from ten to fourteen days the vitamin C value of the unknown is estimated by comparing the growth response with that obtained by feeding a like series of animals with graded amounts of pure ascorbic acid. Thus, with a continuous supply of guinea pigs acquiring scurvy, a test is completed in about two weeks. Care must be exercised in selecting animals for this test, because those which are "too sick" or which show signs of infection will not respond uniformly.

Tooth Method.—Höjer [10] has proposed a method based on the observation that the degree of scurvy can be estimated by histologic examination of the teeth. A cross section of the root of a normal guinea pig incisor shows a row of long parallel odontoblasts surrounding the pulp and active in the formation of dentin. Höjer has described ten stages in the development of scurvy based on the amount of disorganization of the odontoblasts, the width, irregularity and structure of the dentin and the degree of calcification of the predentin. Key and Elphick [11] have described a modification in which, by the same criteria, they distinguish four degrees of scurvy. Using a large series of animals receiving graded doses of ascorbic acid, they plot the average degree of protection against the size of the dose, thus deriving a curve which shows the ratio of protection to dose at any level. When once established, this curve of reference may be used for calculations in successive assays, although it may be revised as additional data accumulate. An example will best show how this curve is used for a determination: A group of healthy growing guinea pigs (from 250 to 300 Gm.) were kept for a few days on a scorbutic diet plus greens. The test was started by withholding the greens. After three days one group of six animals received 0.9 mg. daily of ascorbic acid (International standard). Another group of six animals received 1 cc. of test material (orange juice) daily. Two guinea pigs were kept on the basal diet only (negative control animals). After fourteen days all the animals were killed and the lower jaws fixed and decalcified in 5 per cent trichloroacetic acid, embedded in celloidin and sectioned just anterior and parallel to the first molar at right angles to the longitudinal axis of the mandible. This method gives a cross section of the incisor root, which runs parallel with the jaw at this point.[12] Sections were stained with hematoxylin and eosin and with connective tissue stains. The degree of protection was scored from 1 to 4 for each tooth and the average obtained for all animals on a like level. The guinea pigs receiving the orange juice showed an average protection of 1.3, while those receiving the ascorbic acid averaged 1.8. On the basis of a curve previously prepared as described by Key,[13] the ratio of the protection in terms of ascorbic acid was found to be 0.62 divided by 0.90, which equals 0.69. Since, by definition, 1 mg. of ascorbic acid equals 20 international units, the potency of the orange juice equaled 13.8 international units per cubic centimeter. The curve of response is a device for calculating the relative potency of two materials which do not give an identical response.[14] The feeding of a standard with each assay makes possible a correction for differences in sensitivity of different stocks.[4]

Comparison of Methods.—The chief source of uncertainty in such quantitative methods lies in the unavoidable variation of individual experimental animals and in the indefinite nature of the end point. Complete protection from scurvy or a definite degree of partial protection are conditions difficult to judge. The answer to the problem of which is the best method of bio-assay for vitamin C depends on the experience of the investigator, equipment available, material to be tested, time available, purpose of the assay and many other factors. In addition to the economy of time, the tooth method or the curative method is most useful if the quantity of test material is limited or subject to change by storage. The specificity of the tooth method and the Sherman method is an important feature lacking from the growth response method of Harris. On the other hand, the two former methods are liable to cause subjective errors in judging the degree of scurvy. The need of histologic experience and special equipment for the tooth method are objections to its general use, while the other methods are adaptable to the usual laboratory equipment. It is my experience [15] and that of others [16] that a longer test period than that recommended by Harris (e.g., four weeks) is necessary to obtain quantitative results comparable with those of other methods.

CHEMICAL METHODS

In general, chemical methods are more rapid and accurate than biologic methods but may lack specificity. However, when available and used with precaution they are of great help in many problems not subject to study by bio-assay.

7. A Sherman unit, or a minimum protective dose, is equivalent to 0.5 to 0.6 mg. of ascorbic acid.

8. International standards for assay purposes are obtained by application to the Protein and Nutrition Division, Bureau of Chemistry and Soils, U. S. Department of Agriculture, or to E. Fullerton Cook, Forty-Third Street and Woodland Avenue, Philadelphia.

9. Harris, L. J.; Mills, J. I., and Innes, J. R. M.: The Chemical Identification of Vitamin C, Lancet **2**: 235 (July 30) 1932. Harris, L. J., and Ray, S. R.: Vitamin C in the Suprarenal Medulla, Biochem. J. **27**: 2006 (June) 1933.

10. Höjer, J. A.: Method for Determining the Antiscorbutic Value of Foodstuffs by Means of Histologic Examination of the Teeth of Young Guinea Pigs, Brit. J. Exper. Path. **7**: 356 (Dec.) 1926. Sherman and Smith.[2]

11. Key, Kathleen, M., and Elphick, G. K.: A Quantitative Method for the Determination of Vitamin C, Biochem. J. **25**: 888 (March) 1931. Key and Morgan.[18]

12. It is important that the section be made at a consistent level of the tooth, otherwise the degenerating odontoblasts which normally occur in the incisal part of the tooth may be confused with the scorbutic process. In a longitudinal section of a guinea pig tooth may be observed dental tissue in all stages of development. In the root the odontoblasts are young, regularly arranged and active in the formation of dentin; as they proceed up the persistently growing tooth, a normal sequence of senility and degeneration occurs. Near the biting end of the tooth the odontoblasts normally have much the same appearance as those which are present in the root in scurvy.

13. Key, Kathleen M., and Morgan, Barbara G. E.: The Determination of the Vitamin C Value of Ascorbic Acid, Biochem. J. **27**: 1030 (April) 1933. Coward and Kassner.[16]

14. Coward, Katherine H.: The Biological Standardization of Vitamins, Nutrition Abstr. & Rev. **4**: 24 (April) 1935. Daniel and Munsell.[4]

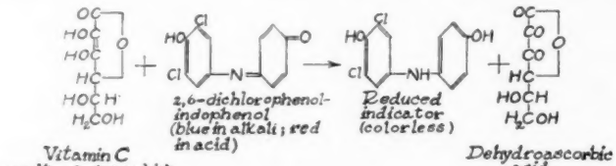
15. Bessey, O. A.: Unpublished data.

16. Coward, Katherine, and Kassner, Elsie W.: The Determination of Vitamin C by Means of Its Influence on the Body Weight of Guinea Pigs, Biochem. J. **30**: 1719 (Sept.) 1936.

The identification of vitamin C as a substance with striking reducing properties made it apparent that it had been studied previously as an unknown reducing substance in plant and animal tissues.[17] Tillmans[18] in studies of the freshness of natural foodstuffs had pointed out that a reducing substance is present in fresh fruits and vegetables which can be estimated by titration against an indicator, 2,6,dichlorophenolindophenol, and which appears to run parallel with their reported vitamin C content. The establishment of the identity of vitamin C by Waugh and King[19] stimulated experiments by Tillmans and his associates,[20] Harris and his associates[21] and Bessey and King[22] which showed the close correlation between the amounts of vitamin C as determined by biological assay and by titration with 2,6,dichlorophenolindophenol in many plant and animal tissues. Additional evidence has supported the view that the titration test when properly used is reasonably specific for vitamin C in natural products.[23]

The essential features of the test are an extraction of the material under examination with an acid-precipitating agent to remove certain interfering substances and to stabilize and bring into solution the vitamin C and subsequent titration of the vitamin with a standardized indophenol solution.

The use of 2,6,dichlorophenolindophenol[22] to determine vitamin C is based on the fact that the colored


2,6-dichlorophenol-indophenol (blue in alkali; red in acid)
Reduced indicator (colorless)
Vitamin C cevitamic (ascorbic) acid
Dehydroascorbic acid

Reduction of indicator solution by vitamin C in acid solution.

indicator solution is quantitatively and rapidly reduced by vitamin C in acid solution to a colorless compound, as represented in the equation.

Indophenol Method.[24]—The indicator solution is prepared by dissolving the required amount of dry dye in hot water (50 mg. for food and 10 mg. for blood or urine per hundred cubic centimeters). Although the solid dye is stable, the aqueous solution slowly changes even when kept in the refrigerator and for this reason should be restandardized frequently. It is standardized against a carefully prepared solution of ascorbic acid containing 20 ± 0.1 mg. per hundred cubic centimeters of 3 per cent metaphosphoric acid.[25] A good commercial ascorbic acid is usually sufficiently pure for this purpose. However, the purity should be checked frequently by titration with iodine.[22] One should dilute 5 cc. of the aforementioned solution to 100 cc. with 3 per cent metaphosphoric acid for standardizing the more dilute dye solution. The strength of the reagent is expressed in milligrams of ascorbic acid per cubic centimeter of indophenol solution.

Extracts of plant and animal tissues for vitamin C determinations are best obtained by thoroughly rupturing the cellular structures in metaphosphoric acid. The acid prevents the rapid oxidation of vitamin C due to enzymes[26] liberated by the macerated cells or by the presence of traces of certain metals.[27] Metaphosphoric acid[28] has replaced the use of other acid-extracting reagents because of its marked protective properties and its inertness toward the indicator. Trichloroacetic acid causes fading of the indicator, which may be very rapid with some batches.[29] Sulfuric acid reacts with the dye and should never be used.[15] Tungstic acid[30] has been used in blood determinations and, although it is a more complete protein precipitant, lacks the protective characteristics of metaphosphoric acid.

An extract of a representative portion of the plant or animal tissue under examination (from 5 to 10 Gm.) is prepared by grinding in a small mortar with sand and fresh 3 per cent metaphosphoric acid until a thin paste is formed. The solids are thrown down in a centrifuge and the clear extract is decanted. Another portion of extracting liquid is used to wash the mortar and is stirred into the solids, which are again centrifuged. The rinsing and washing process is repeated, and the decanted aliquots of the extracts are diluted to 50 cc. Aliquots (10 cc.) of the extracts are titrated with the standard 2,6,dichlorophenolindophenol solution until a faint pink end point is reached. A 10 cc. microburet graduated in 0.01 cc. is convenient.

The indophenol reacts rapidly with vitamin C and should be dropped in at a brisk rate. The end point for most plant tissues is stable for twenty seconds or more, while animal tissues usually fade after from ten to fifteen seconds because of a slow reaction by other substances. Such extracts should be titrated only to an end point at which rapid fading ceases. A correction for the amount of dye required to bring 10 cc. of the extracting acid to the same end point should be applied to all determinations, including the standardizations. This quantity is greater than the usual indicator corrections and should never be neglected. The results are most conveniently expressed in terms of milligrams of ascorbic acid per hundred grams of fresh weight, but in studying vitamin C in tissues which vary considerably in water content, one may get a clearer picture by basing the analysis on dry weight.

Comment.—Since the indophenol method depends on the reduction of the reagent by vitamin C, many substances having a reducing potential lower than the dye are possible sources of interference. However, most such substances found in natural systems react with the

17. Szent-Györgi, Albert: Observations on the Function of the Peroxadase Systems and the Chemistry of the Adrenal Cortex: Description of a New Carbohydrate System, Biochem. J. **22:** 1387 (July) 1928. Harris, L. J.: Vitamins, in Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press **4:** 347, 1935. Tillmans, Hirsch and Hirsch.[18]

18. Tillmans, J.; Hirsch, P., and Hirsch W.: The Reducing Property of Plant Foods and Its Relation to Vitamin C, Ztschr. f. Untersuch. d. Lebensmitt. **63:** 1 (Jan.) 1932.

19. Waugh, W. A., and King, C. G.: The Chemical Nature of Vitamin C, Science **75:** 357 (April 1) 1932; The Isolation and Identification of Vitamin C, J. Biol. Chem. **97:** 325 (April) 1932. Harris, L. J.: Vitamins, in Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press **1:** 357, 1932; **2:** 263, 1933.

20. Tillmans, J.; Hirsch, P., and Vanbel, R.: The Reducing Value of Plant Tissues and Its Indication of Vitamin C, Ztschr. f. Untersuch. d. Lebensmitt. **65:** 145 (Feb.) 1933.

21. Harris, L. J., and Ray, S. N.: Specificity of Hexuronic (Ascorbic) Acid as Antiscorbutic Factor, Biochem. J. **27:** 580 (Feb.) 1933.

22. Bessey, O. A., and King, C. G.: The Distribution of Vitamin C in Plant and Animal Tissues and Its Determination, J. Biol. Chem. **103:** 687 (Dec.) 1933.

23. King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16:** 238 (April) 1936.

24. Harris, L. J.: Vitamins, in Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press **3:** 264, 1934. Harris and Ray.[21] Bessey and King.[22] Musulin and King.[29]

25. Metaphosphoric acid solution is slowly converted to orthophosphoric acid. It should be prepared fresh frequently and should be kept in the refrigerator.

26. Kirtesz, Z. I.; Dearborn, R. B., and Mack, G. L.: Vitamin C in Vegetables: IV. Ascorbic Acid Oxidase, J. Biol. Chem. **116:** 717 (Dec.) 1936. Johnson, S. W., and Zilva, S. S.: The Oxidation of l-Ascorbic Acid by Plant Enzymes, Biochem. J. **31:** 438 (March) 1937.

27. Barron, E. S. G.; DeMeio, R. H., and Klemperer, Friedrich: Biological Oxidation: V. Copper and Hemachromagens as Catalyst for the Oxidation of Ascorbic Acid, J. Biol. Chem. **112:** 625 (Jan.) 1936.

28. Fuijita, Akiji, and Iwatake, Danzo: The Determination of Vitamin C with 2,6-Dichlorophenolindophenol, Biochem. Ztschr. **277:** 293, 1935.

29. Musulin, P. R., and King, C. G.: Metaphosphoric Acid in the Extraction and Titration of Vitamin C, J. Biol. Chem. **116:** 409 (Nov.) 1936.

30. Taylor, F. H. L.; Chase, D., and Faulkner, J. M.: Ascorbic Acid in Serum and Plasma, Biochem. J. **30:** 1119 (July) 1936.

indicator at a perceptibly slower rate than ascorbic acid under the conditions of the titration. This is a requirement for the specificity and accuracy of the method. The end point with plant tissues is stable for some time, but many animal tissue extracts and urines contain sufficient amounts of slow-reducing substances to make the end point less distinct. This is especially true when small quantities of ascorbic acid are being titrated. In such cases the accuracy of the titration depends on the skill of the observer in detecting the point at which rapid reduction is replaced by a slow fading of the indicator. It is true that this feature limits the accuracy of the method, but the precision in most cases is still within the range of biologic variation. The errors are of about the same order as those for blood sugar tests. Unknown reducing materials are reported to interfere with the test in nerve tissue,[31] eye lens and aqueous humor,[32] the liver of some species [33] and tumor tissues.[34] Reduction by phenols, tannins, glutathione and many other substances is eliminated by titration in acid solutions below p_H 3. Cysteine, sometimes present in autolyzed tissue, must be estimated separately or removed from the system. Ergothionine, thiosulfate, cysteine and other organic sulfur compounds may be removed by a rather unpractical mercuric acetate treatment suggested by Emmerie.[35] Reductone (glucic acid),[36] reductic acid [37] and other derivatives formed in hot alkaline sugar solutions reduce the dye in a manner indistinguishable from that of vitamin C. Similar compounds are found in yeast, mold, malt extract and beer.[38] These examples illustrate the point that when one is dealing with a type of material not previously checked it is best to establish the validity of the test by other means.

Recent evidence [38a] suggests that there may exist in certain plant tissues significant quantities of physiologically available combined ascorbic acid which is not extracted by the usual acid extracting reagents and therefore is not included in the titration value. Unless the extracts are carefully prepared and titrated without too much delay, oxidation of vitamin C by liberated enzymes or traces of metals may cause a low titration figure. If the oxidation has proceeded beyond the first step as previously indicated,[39] both the chemical and the biologic value will be low. In general, reversibly oxidized ascorbic acid (dehydroascorbic acid) represents an insignificant portion of the total biologic value of fresh or storage products.

The titration value of some tissue extracts may be increased by preliminary treatment with hydrogen sulfide.[35] Some investigators have interpreted this increase as due to reduction of dehydroascorbic acid and have modified the method to include both forms of ascorbic acid. There is some doubt whether it is due to the reduction of dehydroascorbic acid or to the reduction of other substances which are then included in the titration. The uncertainty of the procedure is also increased by the necessity of completely removing the gas because hydrogen sulfide also reduces the indicator. Emmerie and Van Eekelen recommended the use of mercuric acetate to remove cysteine ergothionine and of thiosulfate followed by treatment with hydrogen sulfide. The extra manipulation involved, with uncertainty at every step, makes the method at present of doubtful value.

Microtitration with indophenol for special purposes has been described by Birch, Harris and Ray,[40] Farmer and Abt [41] and Glick.[42] The last named has applied the Linderstrom technic to microtome-cut sections of glandular tissues with some success.

Other Chemical Methods.—Alternative methods based on the reduction of ferrocyanide,[43] phosphotungstic acid,[44] methylene blue [45] phosphomolybdic acid [46] and other color reagents have been proposed. From a theoretical standpoint it would seem that these reagents might be as specific and useful as indophenol, but for one reason or another they have not been widely adopted. In some cases they react too slowly in acid solutions (p_H from 2 to 3 is a necessary condition for specificity). The color changes often vary with time. Many of these reagents react quantitatively with pure ascorbic acid solution but are inhibited or reduced by other materials in urine and tissue extracts. Ascorbic acid in some cases shows side reactions with the reagent, thus interfering with quantitative reduction. A spectroscopic method [47] in which the intensity of absorption (265 millimicrons) is measured before and after the destruction of the vitamin has been of value in checking the accuracy of the indophenol method. Extracts require special attention in removing irrelevant absorbing materials. Tauber and Kleiner [48] advocated the determination of reducing capacity before and after the destruction of the vitamin by an oxidase as a means of increasing the specificity of the test. This method is also not entirely specific, because of the nonspecificity of the

31. Young, F. G., and Mitolo, M.: A Reducing Substance in Brain Tissue. Nature **133:** 572 (April) 1934. Plant, F.; Bülow, M., and Pruckner, F.: Chemical and Spectroscopic Comparison of the Vitamin C Content of Urine, Spinal Fluid and Serum, Ztschr. f. physiol. Chem. **234:** 131 (April) 1935.

32. Birch, T. W., and Dann, W. J.: Ascorbic Acid in Eye Lens and Aqueous Humor of the Ox, Biochem. J. **28:** 638, 1934. von Euler, Hans, and Malmberg, May: Antiscorbutic Action of the Eye Lens and Its Contents of Reductone and Sulphydryl Compounds, Ztschr. f. physiol. Chem. **230:** 225, 1934.

33. Borsook, Henry; Davenport, H. W.; Jeffreys, C. E. P., and Warner, R. C.: The Oxidation of Ascorbic Acid and Its Reduction in Vitro and in Vivo, J. Biol. Chem. **117:** 237 (Jan.) 1937.

34. Kellie, A. E., and Zilva, S. S.: The Identity of the Indophenol Reducing Substance in the Jansen Sarcoma, Biochem. J. **30:** 1216 (July) 1936. Harris, L. J.: A Reducing Substance in Tumor, Nature **132:** 605 (Oct.) 1933. Harris.[34]

35. Emmerie, Adrianus: Separation of Cysteine from Ascorbic Acid by Mercuric Acetate, Biochem. J. **28:** 268, 1934. Emmerie, Adrianus, and Van Eekelen, Marie: The Chemical Determination of Vitamin C with Removal of Interfering Reducing and Colored Substance, ibid. **28:** 1153, 1934; Some Critical Remarks on the Determination of Ascorbic Acid, ibid. **30:** 25 (Jan.) 1936.

36. Nelson, E. K., and Browne, C. A.: The Properties and Chemical Constitution of Glucic Acid, J. Am. Chem. Soc. **51:** 830 (March) 1929. von Euler, Hans, and Martius, Carl: Reductone and Ascorbic Acid, Ann. d. Chem. **505:** 73, 1933. King.[36] Nelson and Mottern.[19]

37. Reichstein, T., and Oppenhauer, R.: Reductic Acid: A Strong Reducing Split Product of Carbohydrates, Helvet. chim. Acta. **17:** 390, 1934.

38. Harris, L. J.: Chemical Tests for Vitamin C and the Reducing Substances Present in Urine and Other Tissues, Nature **132:** 27 (July) 1933. von Euler.[3] Fox and Stone.[49]

38a. Reedman, E. J., and McHenry, E. W.: Combined Ascorbic Acid in Plant Tissues, Biochem. J. **32:** 85 (Jan.) 1938.

39. Borsook and his co-workers.[33] King.[50]

40. Birch, T. W.; Harris, L. J., and Ray, S. N.: A Microchemical Method for Determining the Hexuronic Acid (Vitamin C) Content of Foodstuffs, Biochem. J. **27:** 590, 1933.

41. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34:** 146 (March) 1936.

42. Glick, David, and Biskind, G. R.: The Histochemistry of the Adrenal Gland: I. The Quantitative Distribution of Vitamin C, J. Biol. Chem. **110:** 1 (June) 1935; The Histochemistry of the Hypophysis Cerebri: The Quantitative Distribution of Vitamin C, ibid. **110:** 583 (Aug.) 1935.

43. Tauber, Henry, and Kleiner, T. S.: A Method for the Quantitative Determination of Ascorbic Acid (Vitamin C), J. Biol. Chem. **108:** 563 (Feb.) 1935.

44. Medes, Grace: The Determination of Ascorbic Acid in Urine with Phospho-18-Tungstic Acid, J. Biochem. **29:** 2251 (Oct.) 1935.

45. Cál, Imre: Estimation of Ascorbic Acid by Titration, Nature **138:** 799 (Nov.) 1936.

46. Bezssonoff, N.: Sur l'identification de la vitamine C, Bull. Soc. chim. Biol. **16:** 1107 (July, Aug.) 1934. Bezssonoff, N.; DeLire, A., and Van Wien, H.: L'activité réductrice de la vitamine C et d'autres réducteurs biologiques exprimée en fonction de leur concentration, ibid., p. 1133. Bezssonoff, N., and Van Wien, H.: Sur l'identification et le dosage de la vitamine C dans les milieux biologiques, ibid., p. 1160. von Euler, Hans, and Burstrom, Dagmar: Ascorbic Acid Determinations in Urine by Titration, Biochem. Ztschr. **283:** 153, 1936.

47. Robertson, E. B.: Spectroscopic Estimation of Ascorbic Acid, J. Chem. Industry **53:** 277 (March) 1934. Chevallier, André, and Choron, Yvonne: Spectrophotometric Method for Estimating Vitamin C in Tissues, Compt. rend. Soc. de biol. **125:** 65, 1937.

48. Tauber, Henry, and Kleiner, I. S.: An Enzymic Method for the Estimation of True Vitamin C, J. Biol. Chem. **110:** 559 (Aug.) 1935.

enzyme.[49] Roe [50] has described a method based on another principle, the color reaction between aniline acetate and furfural, a decomposition product of ascorbic acid.

In general the special features of these procedures are outweighed by features which make them less straightforward and less specific than the indophenol method. A discussion of the weaknesses and merits of all the proposed chemical methods is not within the realm of this paper.

Urine Technic.[51]—The excretion of vitamin C in the urine depends primarily on the relative degree of saturation of the tissues and the immediate intake of ascorbic acid. As a state of tissue saturation is approached, the quantity of ascorbic acid excreted in the urine gradually increases until at saturation a marked abrupt elevation occurs. The quantity of ascorbic acid required to induce saturation appears to be a measure of the state of vitamin C nutrition of the patient.[3c]

The analytic procedure for urine is essentially the same as that previously described for tissues. Each specimen of voided urine is measured and a 50 cc. volume containing 10 cc. of 20 per cent metaphosphoric acid is filled to the mark and stoppered. Aliquots should be stored in the refrigerator and titrated within eight to ten hours, during which time relatively little loss occurs. For analysis, the specimen is centrifuged if cloudy, and from 2 to 5 cc., depending on the concentration of ascorbic acid, is diluted to 10 cc. with 3 per cent metaphosphoric acid. The mixture is quickly titrated to a definite pink end point against a standard indophenol solution, a microburet being used. After correction for the titration blank and the added metaphosphoric acid, the total excretion of the specimen is estimated and the twenty-four hour output calculated. The reducing capacity of the urine collected during a preliminary period before the test establishes the excretion level of the patient before treatment with ascorbic acid. This also places the interpretation of the test on a comparative basis, thus correcting for the small constant effect of reducing substances other than ascorbic acid usually present in the urine.[52] Heinemann [53] has reported a significant interference by thiosulfate, especially when the diet is high in protein. However, the virtual disappearance of the reducing value in cases of scurvy and extreme deficiency and its restoration at a predicted rate when ascorbic acid is fed contribute strong evidence for the accuracy of the test. Provided manipulations are carried out properly and interpretations of too fine a character are not attempted, the method is of real value.

The estimation of the excretion of ascorbic acid before and after a single dose is also of value in demonstrating the presence of subnutrition of vitamin C. This procedure undoubtedly shows the absence of saturation, but sufficient data have not been collected to allow for an estimation of the degree of deficiency such as is possible by the repeated dose method.

Blood Technic.[54]—The vitamin C level of normal blood plasma as estimated by titration shows a close correlation with the level of intake, thus providing means for evaluating the reserve vitamin C by a single determination for persons in that wide zone between scurvy and saturation (from 0.3 to 1.8 mg. per hundred cubic centimeters). This rapid direct application of the test will undoubtedly replace the less practical urine technic for many purposes.

With slight variations, the procedure now most widely used for blood titrations is as follows: Five or more cubic centimeters of blood is oxalated in a tube which also contains 2 mg. of potassium cyanide, and 2 cc. of plasma is pipeted into 8 cc. of 3 per cent metaphosphoric acid solution. The mixture is stirred, stoppered and centrifuged. A 5 cc. aliquot (equal to 1 cc. of plasma) of the clear centrifugate is immediately titrated, as previously described, with dilute 2,6,dichlorophenolindophenol. After a correction for the blank, which always should be performed parallel with a determination, the ascorbic acid is calculated and expressed as milligrams per hundred cubic centimeters of plasma. All sources of error being taken into consideration, the titration is probably within 0.1 to 0.2 mg. of the true ascorbic acid content of the blood for the range from 0.3 to 1.8 mg. per hundred cubic centimeters. With plasma of lower value, the errors are greater. Cyanide is added to inhibit the slow inactivation of ascorbic acid which occurs in both plasma and filtrate. This is a good precautionary measure against oxidation due to traces of copper and other catalysts, although I have never observed such high rates of destruction in the absence of cyanide as have been reported.[55] With carefully prepared reagents and water redistilled from glass, the filtrates remain stable for several hours. Metaphosphoric acid is preferred as a deproteinizing agent for reasons previously stated. Plasma is preferred to whole blood for vitamin C determinations because of the greater stability of plasma filtrates.[56] Substances liberated from red cells by deproteinizing reagents catalyze the inactivation of ascorbic acid even in the presence of cyanide. For this reason plasma which shows evidence of hemolysis is unsuitable for ascorbic acid determinations. Another objection to using whole blood filtrates for vitamin C titration arises from liberation of substances that also reduce the dye. This becomes especially significant when the filtrate is treated with hydrogen sulfide before titration, as recommended by some investigators.

A satisfactory method requiring less blood would be of distinct value in preventing the necessity of venous puncture. Micromethods so far published have not been a solution to this problem. The chief difficulty of titrating such small quantities lies with the inaccuracies of the end point determinations. Mindlin and Butler,[57] in an unpublished manuscript, propose a method which yields results satisfactory for clinical purposes by the use of from 0.2 to 0.3 cc. of capillary blood. The decrease in concentration of colored indicator produced by the addition of an amount of blood plasma filtrate insufficient to cause complete reduction of the dye is

49. Fox, F. W., and Stone, William: Specificity of Indophenol in the Estimation of Ascorbic Acid in Fermented Products, Nature **140:** 234 (Aug.) 1937. Johnson and Zilva.[24] King.[59]

50. Roe, J. H.: The Determination of Ascorbic Acid as Furfural and a Comparison of Results Obtained by This Method and by Indophenol Titration, J. Biol. Chem. **116:** 609 (Dec.) 1936.

51. Sendroy, Julius, Jr., and Schultz, M. P.: Studies of Ascorbic Acid and Rheumatic Fever: I. Quantitative Index of Ascorbic Acid Utilization in Human Beings and Its Application to the Study of Rheumatic Fever, J. Clin. Investigation **15:** 3691 (July) 1936. Harris, L. J., and Ray, S. N.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, Lancet **1:** 71 (Jan. 12) 1935. Albasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin-C Subnutrition by Urine Analysis, Lancet **2:** 1399 (Dec. 21) 1936. von Euler.[3] Sherman and Sherman.[3]

52. Borsook and his co-workers.[33] Heinemann.[53]

53. Heinemann, M.: Dietary Influence on the Amount of Ascorbic Acid and Other Reducing Substances in Urine, Acta brev. Neerland. **6:** 67 (Aug.) 1936.

54. Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic (Ascorbic Acid) Determinations in Blood Plasma and Their Relationship to Capillary Resistance, J. Pediat. **8:** 1 (Jan.) 1936. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10:** 577 (May) 1937. Sherman and Sherman.[3] Bessey.[15] Farmer and Abt.[41] Pijoan and Klemperer.[55]

55. Pijoan, Michel, and Klemperer, Friedrich: Determination of Blood Ascorbic Acid, J. Clin. Investigation **14:** 443 (May) 1937.

56. Borsook and his co-workers.[33] Farmer and Abt.[41]

57. Mindlin, R. L., and Butler, A. M.: The Determination of Ascorbic Acid in Plasma: A Macro and Micro Method, J. Biol. Chem. **122:** 673? (Feb.) 1938.

measured by means of a photo-electric colorimeter. This eliminates the subjective reading of the end point. An accurately standardized dye is not needed. Observation of the rate of fading of the color with time permits the detection and study of reducing substances reacting at a slower rate than ascorbic acid.

It is important to emphasize the fact that titrations of blood and many other tissues which are extremely low in ascorbic acid have a limited accuracy even when done with the greatest care. A disregard for this fact is apparent from published investigations. Conclusions based on differences far smaller than the errors of the method used are obviously of doubtful value. Such misinterpretation can be avoided only by a thorough understanding and proper application of the technic.

DIETARY SOURCES

This discussion is concerned with the distribution of vitamin C in food and necessarily lays emphasis on this subject. It should be remembered that adequate nutrition is a problem of supplying many factors in proper proportions and can be met only by use of a variety of foods. Condemnation of a food product because it possesses a low vitamin C value, unless this is a consequence of improper processing or handling, is unjustified. Some foods with many excellent nutritional properties are naturally of low antiscorbutic value.

Ascorbic acid value as far as nutrition is concerned is dependent primarily on two factors: (1) the natural potency of the particular plant or animal tissue and (2) the consequence of aging and processing which occurs before its use as food.

Among the richest sources of vitamin C are oranges, lemons, grapefruit (raw or canned), tangerines, tomatoes (raw or canned) fresh strawberries, green peppers and raw cabbage.[58]

Properly prepared green leafy vegetables have good vitamin C value in spite of the relatively large losses from cooking or canning. In this group may be classed cabbage, spinach, brussels sprouts, kale, broccoli and vegetable greens, such as turnip, beet and dandelion.

Apples, bananas, pineapples (canned), potatoes, green beans and green peas, although containing less antiscorbutic activity, are important sources because of the quantities included in the diet.

The lettuce group, including escarole, have a lower vitamin C content than is generally realized but, since they are usually consumed raw, compare favorably with cooked vegetables. Other important vitamin C-containing foods are kohlrabi, onions, turnips, parsnips and cauliflower.

Dry cereals and legumes of all varieties are devoid of vitamin C, but almost any seed soaked in water for twenty-four hours and kept moist for a few days until it sprouts becomes an effective antiscorbutic substance even when cooked. The British committee on accessory food factors has recommended the use of sprouting seeds as antiscorbutic foods in times of famine.

Cooked muscle meat [2] is practically free from ascorbic acid, although experience seems to show that if consumed rare or raw in large quantities it prevents scurvy. Liver is greatly superior to muscle in this respect. The distribution of vitamin C in other animal tissues (not important as food) has been discussed in a previous paper of this series.[59]

Butter, eggs and cheese contain no vitamin C. The vitamin C value of commercial pasteurized milk is very small.

58. Sherman and Smith.[2] Daniel and Munsell.[4] Fellers.[68] Sherman.[83]
59. King, C. G.: Vitamin C Chemistry, J. A. M. A., to be published.

Variety.[60]—Before the introduction of the chemical method, it was not practical to undertake any comprehensive study of the influence of various factors such as variety, type of soil, season and maturity on the vitamin C potency of fruits and vegetables. Enough information has been obtained now to indicate clearly the need of attention to these points in attempting to obtain food of the highest antiscorbutic value.

Certain varieties of tomatoes [61] contain double the quantity of vitamin C of others grown on the same soil under the same conditions. Canners of tomato juice should give as much attention to this fact as to methods of processing in order to provide the most potent product. Some varieties of apples [62] are definitely higher in antiscorbutic value than other varieties. Similar consistent differences according to variety have been reported for spinach,[63] cabbage,[64] beans and peas [65] and probably exist for most fruits and vegetables.

Soil conditions affect the vitamin C content of spinach. Several varieties grown on upland soil were found to average 50 per cent richer than the same varieties grown on muck soil when compared under otherwise similar conditions.[66] Fall spinach when compared with the same varieties grown in the spring was found to be appreciably higher in ascorbic acid content. It therefore seems likely that crops from year to year may vary in ascorbic acid value because of conditions such as moisture and temperature.

Maturity and Origin.—Tomatoes increase somewhat in vitamin C content as the fruit ripens.[67] However, mature green tomatoes may have nearly the same value as the red ripe fruit.[68] The ascorbic acid content of green peppers increases considerably on reddening. A single fruit which is green on one side and red on the other may show a difference of as much as 75 per cent.[69] A lower vitamin C content in oranges sprayed with lead arsenate has been reported.[70] Immature Bramley seedling apples are as rich in vitamin C as mature fruit.[68] Most green leafy and root vegetables contain the greatest concentration of vitamin C during the period of most rapid growth. Sweet corn [71] and green peas [72] show a maximum vitamin C content during the tender stage, and the content decreases as the seed matures. This is consistent with the lack of vitamin C in nonrespiring mature seeds. Ethylene ripening itself has no effect but tends to encourage early picking and may lead to a slightly lower vitamin C value due to immaturity.[73]

How and from what most plants and some animals form ascorbic acid is not clear, but the distribution in animal tissues shows it to occur in the greatest concentration in the most actively functioning tissues, in the

60. Daniel and Munsell.[4] Fellers.[68] Tressler, Mack and King.[75]
61. Tripp, Francis; Satterfield, G. H., and Holmes, A. D.: Varietal Differences in the Vitamin C (Ascorbic Acid) Content of Tomatoes, J. Home Econ. **29:** 258 (April) 1937. Maclinn, Fellers and Buck.[77]
62. Smith, G. G., and Fellers, C. R.: Vitamin C Content of Twenty-One Massachusetts Grown Varieties of Apples, Proc. Am. Soc. Horticultural Sc. **31:** 89, 1934. Batchelder.[76]
63. Tressler, D. K.; Mack, G. L., and King, C. G.: Vitamin C Content of Vegetables: I. Spinach, Food Research **1:** 3 (Feb.) 1936.
64. Gould, Stella; Tressler, D. K., and King, C. G.: Vitamin C Content of Vegetables: V. Cabbage, Food Research **1:** 427 (Oct.) 1936.
65. Mack, Tressler and King, footnotes 72 and 75.
66. von Hahn, F. V., and Gorbling, J.: Influence of Fertilizer on the Vitamin C Content of Spinach, Ztschr. f. Untersuch. Lebensmitt. **65:** 601 (April-June) 1933. Tressler, Mack and King.[63]
67. Sherman and Smith.[2] Tripp, Satterfield and Holmes.[61]
68. Fellers, C. R.: The Effect of Processing in Fruit and Vegetables: A Review, Bull. 338, Massachusetts State College Agricultural Experiment Station, Amherst, December 1936.
69. Bessey and King.[22]
70. Nelson, E. M., and Mottern, H. H.: Effect of Lead Arsenate Spray on the Composition and Vitamin Content of Oranges, Am. J. Pub. Health **22:** 587 (June) 1932.
71. Dunker, C. F.; Fellers, C. R., and Fitzgerald, G. A.: Stability of Vitamin C in Sweet Corn, Food Research **2:** 41 (Jan.) 1937.
72. Mack, G. L.; Tressler, D. K., and King, C. G.: Vitamin C Content of Vegetables: II. Peas, Food Research **1:** 231 (May) 1936.
73. Chace, E. M.: Health Problems Connected with Ethylene Treatment of Fruit, Am. J. Pub. Health **24:** 1152 (Nov.) 1934.

adrenal cortex, corpus luteum, thyroid, pituitary body and liver. This distribution proves to be true also in leaves and growing shoots and suggests a fundamental concern with respiratory processes. However, many rapidly growing fruits are low in ascorbic acid, and the respiratory activity of lemons, oranges and tomatoes does not seem to be unusually high, although these are among the richest sources of ascorbic acid. Eggs and seeds are devoid of vitamin C, but the vitamin forms immediately from unknown constituents when a chick embryo develops or the seed sprouts.

Storage.[68]—Time, temperature, care in handling and type of product are important factors in the problem of the stability of vitamin C during storage. Spinach which has stood for a few days at room temperature and has become wilted loses about one half of its ascorbic acid, while the same spinach kept at 37 or 38 F. for the same period retains its original value.[74] This is true in general of green leafy vegetables of this type. Cabbage stored at room temperature loses about 25 per cent of its vitamin C in a month, while at 45 or 50 F. the loss is only 10 per cent.[64] Green beans and peas, like spinach, rapidly lose their ascorbic acid at room temperature but keep well by refrigeration.[75] Sweet corn in the husk retains its vitamin C well for two or three days, after which time a slow loss occurs.[68] Green peppers remain rich sources of ascorbic acid for several weeks if they do not become bruised or wilted.[15] Loss in apples after three months at 45 F. approximates 15 per cent, at six months 25 per cent and at one year 50 per cent.[76] Lemons and oranges stored at 45 or 50 F. for ten months show losses of from 10 to 30 per cent; no detectable loss occurs in two months.[15] Storage of ripe tomatoes at ordinary temperature for a month causes little change in the vitamin C content provided the fruit remains firm and free from bruises and rot.[77] Potatoes very slowly lose their vitamin C under market conditions; about a 50 per cent loss occurs in one year.[22] With some varieties, little loss is observed after from three to six months' storage.[78] Vitamin C in rutabagas, carrots, turnips and sweet potatoes is slowly lost over a period of several months.[68]

These facts demonstrate the great variation in "storage stability" of vitamin C and indicate the advantage of cold storage as compared with ordinary storage.

Freezing.—Preservation of fruits and vegetables by quick freezing has become an important commercial method.[79] Studies on the stability of vitamin C during freezing and storage in general have shown slight destruction, but often incidental processing operations such as shelling, washing and blanching lead to significant losses. Asparagus, apples, potatoes, strawberries, blackberries and orange juice are unaffected by freezing, while some losses are reported in preparatory operation with peas, beans and spinach. Freezing results in a certain amount of cellular disorganization, with liberation of enzymes from some types of plant tissues. Unless these products are properly blanched (to destroy enzymes) before freezing, considerable losses may occur during storage and thawing. Slow-thawing vegetables rapidly lost their vitamin C. Losses of from 80 to 90 per cent may occur in beans, peas or spinach in a few hours. Frozen foods should not be defrosted until ready to cook or serve raw. Losses are reduced to a minimum by cooking without preliminary defrosting.

Processing.—For several reasons, effort should be made to conserve the vitamin C values of the general food supply rather than to depend on the use of foods of special antiscorbutic properties. A larger percentage of the people than is generally realized, because of economic conditions, lack of knowledge or poor food habits, do not include citrus fruits, tomatoes or other richly antiscorbutic foods in their diet. These people necessarily depend on the general food supply for their source of this essential. Also the loss of important food qualities, such as flavor and the content of other vitamins, usually parallels the destruction of vitamin C. In fact, the preservation of ascorbic acid may well be used as a general index to the care with which certain foods have been processed.

The preservation of vitamin C between harvesting and consumption is essentially a problem of combating oxidation, a process dependent on time and the kind and state of the tissue and influenced by temperature, access to air and presence of metals and enzymes. The destruction of vitamin C when tomato juice is heated can be reduced two thirds by rendering the conditions anaerobic.[80] Spinach and cabbage cooked by methods excluding air are from 50 to 100 per cent richer in vitamin C than when prepared by open kettle cooking.[81] The water in which vegetables are cooked may contain sufficient oxygen to become an important factor of destruction.[82] This fact has led to the practice of starting vegetables in hot water.

Crushing or bruising of many vegetables such as spinach, cabbage, turnips and rutabagas causes the liberation of enzymes (oxidases) which in the presence of air catalyze the oxidation of ascorbic acid.[26] This is a rapid reaction and may lead to complete inactivation of the injured tissue in a few minutes. Starting the cooking in hot water quickly inactivates these enzymes. Shredded carrots, cabbage and other roots and leafy tissues rapidly decrease in vitamin C content and should therefore be prepared fresh before serving.

Vitamin C is more stable in an acid medium than in a neutral or slightly alkaline medium.[83] The addition of soda to cooking vegetables may produce a better color but will lead to increased loss of vitamin C. The vitamin C in tomato juice is naturally stable but becomes rapidly inactivated when neutralized or made alkaline with soda. In general, vitamin C is less subject to oxidation in those fruits and vegetables which are acid.

There is perhaps no single factor which accelerates the destruction of vitamin C so much as copper salts. The presence of air and the merest traces of copper lead to complete inactivation often in a few minutes. Contact with bare copper or utensils made of metal containing copper must be avoided. Quantities of copper so small as to be undetectable by the usual chemical methods will lead to immediate and complete destruction of the ascorbic acid in raw milk or cooking vegetables.[84] The insidious nature of this factor makes it

74. Tressler, Mack and King, footnotes 63 and 75.
75. Tressler, D. K.; Mack, G. I., and King, C. G.: Factors Influencing the Vitamin C Content of Vegetables, Am. J. Pub. Health **26**: 905 (Sept.) 1936.
76. Batchelder, Esther L.: Vitamin C in Apples, J. Nutrition **7**: 647 (June) 1934.
77. Maclinn, W. A.; Fellers, C. R., and Buck, R. E.: Tomato Variety and Strain Differences in Ascorbic Acid (Vitamin C) Contents, Am. Soc. Horticultural Sc. **34**: 543, 1937.
78. Fellers.[68] Wood.[59]
79. Nelson, E. M., and Mottern, H. H.: Vitamin C Content of Frozen Orange Juice, J. Indust. & Engin. Chem. **25**: 216 (Feb.) 1933. Daniel and Munsell.[4] Fellers.[68] Tressler, Mack and King.[75]
80. Kohlman, Eddy and others.[82] Sherman.[83]
81. Sherman and Smith.[2] Bessey.[15]
82. Kohman, E. F.; Eddy, W. H., and Gurin, C. Z.: Vitamins in Canned Foods: XI. A Canned Food Diet, J. Indust. & Engin. Chem. **23**: 1064 (Sept.) 1931; Canning Tomato Juice without Vitamin C Loss, ibid. **25**: 682 (June) 1933.
83. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 5, New York, Macmillan Company, 1937.
84. Whitnah, C. H.; Riddell, W. H., and Caulfield, W. J.: The Influence of Storage, Pasteurization, and Contamination with Metals on the Stability of Vitamin C in Milk, J. Dairy Sc. **19**: 373, 1936. Bessey.[19]

very difficult to control, for, in addition to contamination by contact and from the water supply, many foods naturally contain enough copper to be active.

Drying [85] in itself is not detrimental to vitamin C, but for most foods it is almost impossible to prevent oxidation due to other factors sufficiently to prepare dehydrated products of important and lasting antiscorbutic values. Dehydrated foods have repeatedly failed in this respect when used in times of war. Many experiments have been reported showing that certain of the more acid fruits may be prepared so as to conserve a reasonable degree of their vitamin C activity, but commercial products cannot as yet be considered dependable in this respect.

agreement with the previous emphasis on the unfavorable "influence" of contact with copper utensils, access to air, prolonged heating and alkalinity. Modern commercial canning, with careful plant control, can prepare products with a minimum loss of vitamin C which are comparable to carefully cooked fresh food. However, no rule can cover all cases, for there are badly controlled canneries as well as bad cooks. The variations in processing are so great that the products from each process and perhaps each batch would have to be tested before one could be sure of the vitamin C value. Boiling of cabbage in an open kettle or cooking in a pressure cooker leads to almost complete destruction, while starting the cabbage in boiling water and testing both the

The Vitamin C Content of Various Foods per Hundred Grams *

Food	Mg. of Ascorbic Acid	International Units
Apples		
Delicious	2.5	50
Jonathans	2.5	50
McIntosh	2	40
Winesaps	5	100
Golden delicious	4	80
Yellow Newton	5	100
Dried	0	0
Juice	See type of apple	
Apricots, fresh	1	20
Apricots, dried	8	160
Asparagus	20	400
Bananas	8	160
Beans		
Green	10	200
Green canned	4	80
Sprouted	10	200
Dried	0	0
Beef muscle, cooked	Trace	Trace
Beer	0	0
Beets	5	100
Beet leaves	35	700
Blackberries, fresh	3	60
Blackberries, frozen	3	60
Blueberries, low bush	4	80
Blueberries, high bush	10	200
Broccoli	50	1,000
Brussels sprouts	50	1,000
Butter	0	0
Cabbage, young, green	40	800
Cabbage, old	20	400
Cantaloup	7	140
Carrots	3	60
Cauliflower	30	600
Celery stalk	5	100
Chicory	10	200
Chard, Swiss, stalks	5	100
Chard Swiss, leaves	20	400
Cheese, all varieties	0	0
Cherries, sweet	8	160
Cider, fresh	See apples	
Chicken meat, cooked	Trace	
Cod liver oil	0	0
Collard	60	1,200
Corn		
Sweet	10	200
Canned	6	120
Dried	0	0
Cranberries	10	200
Cucumbers	2	40
Currants, black	100	2,000
Currants, red	15	300
Dandelion greens	40	800
Dates, cured	0	0
Egg plant	5	100
Eggs	0	0
Endive	10	200
Escarole	7	140
Figs, fresh	2	40
Figs, dried	0	0
Fish, fresh cooked	Trace	Trace
Fruit juice	See fruit	
Gooseberries	25	500
Grain, dried, all varieties	0	0
Grass, fresh, green	60	1,200
Grape juice	Trace	Trace
Grapefruit juice, fresh	40	800
Grapefruit juice, canned	30	600
Horseradish	100	2,000
Jelly	0	0
Kale	50	1,000
Kohlrabi	70	1,400
Leek	15	300
Lemon juice		
Fresh	60	1,200
Cold storage	40	800
Canned	50	1,000
Lettuce, green leaf	10	200
Lettuce, head	5	100
Lime juice, fresh	30	600
Liver, beef, cooked	10	200
Malt	0	0
Milk		
Human	6	120
Cow's, raw, fresh	2	40
Cow's, pasteurized	0 to 1	0 to 20
Cow's, dried	5	100
Mustard leaves	60	1,200
Nuts, all kinds	0	0
Okra	10	200
Onion	10	200
Orange juice, fresh	50	1,000
Orange juice, canned	45	900
Orange syrup	0	0
Papaya	40	800
Parsley	175	3,500
Parsnips	5	100
Peas, green	15	300
Peas, canned	5	100
Peaches, fresh	7	140
Peaches, dried	25	500
Pears, fresh	3	60
Pear juice, canned	Trace	Trace
Peppers, green	180	3,600
Peppers, red, ripe	230	4,600
Pineapple, fresh	25	500
Pineapple, canned	10	200
Plums	2	40
Potatoes, new	15	300
Potatoes, old	7	140
Prunes	2	40
Prunes, dried	0	0
Pumpkins	5	100
Quince	5	100
Radishes	12	240
Raisins	0	0
Raspberries	15	300
Rhubarb	15	300
Rutabaga	20	400
Seeds, mature, dry (all varieties)	0	0
Spinach, fresh	60	1,200
Spinach, canned	5 to 10	100 to 200
Sauerkraut juice	0 to 5	0 to 100
Squash	3	60
Strawberries	25	500
Sweet potatoes	8	160
Swede	See rutabaga	
Tangerines	30	600
Tomatoes		
Green	20	400
Vine ripe	30	600
Artificial ripe	25	500
Tomato juice, fresh	30	600
Tomato juice, canned	25	500
Turnips	30	600
Turnip greens	60	1,200
Vegetable juices canned	0 to 5	0 to 100
Watercress	50	1,000
Watermelon	5	100
Yeast	0	0

* Unless otherwise indicated, these values are on fresh foods.

Pickling, salting, curing or fermenting usually results in complete loss of vitamin C. Fresh cucumbers contain from 5 to 8 mg. per hundred grams; salt pickles contain none. Fermented cider and other fruit juices are free from vitamin C. Sauerkraut and sauerkraut juice are unreliable antiscorbutic foods.[86] Commercial orange drinks which do not contain freshly prepared orange juice are practically free from ascorbic acid.[87] Vegetable juices rapidly lose their vitamin C because of active enzymes and a high p_H and therefore are usually poor antiscorbutic foods.

It is difficult to make general statements concerning the loss of vitamin C during such a variable process as cooking [88] or canning. Recent work is in essential agreement with the previous emphasis on the unfavorable "influence" of contact with copper utensils, access to air, prolonged heating and alkalinity. Modern commercial canning, with careful plant control, can prepare products with a minimum loss of vitamin C which are comparable to carefully cooked fresh food. However, no rule can cover all cases, for there are badly controlled canneries as well as bad cooks. The variations in processing are so great that the products from each process and perhaps each batch would have to be tested before one could be sure of the vitamin C value. Boiling of cabbage in an open kettle or cooking in a pressure cooker leads to almost complete destruction, while starting the cabbage in boiling water and testing both the cooking water and the cabbage produce about 25 per cent destruction and 25 per cent loss in the water.[64] Similar studies on spinach, turnip greens and green peas and beans lead to approximately the same conclusions. Commercial canning destroys from 50 to 85 per cent of the vitamin C in peas, lima beans, spinach and asparagus. Home-canned tomato juice is as satisfactory as commercial canned juice, and both are good antiscorbutic substances.[2] Vitamin C is stabilized by acid and therefore suffers less destruction during cooking in acid fruits and vegetables. Canned grapefruit and orange juice are about 70 to 90 per cent as potent as the fresh juice and, like most canned products, remain stable while canned but slowly lose their vitamin C when left open to the air.[87] Baked and boiled potatoes are reported to show only small losses unless overcooked.[89] Fruit jel-

85. Fellers.[63] Sherman.[83]
86. Sherman and Smith.[2] Fellers.[63]
87. Bessey.[35] Fellers.[64]
88. Sherman and Smith.[2] Gould, Tressler and King.[61] Fellers.[63] Sherman.[83]

89. Wood, E.: The Vitamin C Content of the Russel Burbank Potato of Idaho, Bull. 219, University of Idaho Agricultural Experiment Station, June 1935. Fellers.[63]

lies and jams are usually low in vitamin C. Warmed over foods are practically free from ascorbic acid. Canned or cooked apricots, peaches, plums and cherries are practically free from vitamin C. Freshly prepared apple sauce or apple pies retain from 20 to 30 per cent of the original vitamin C value of the apple.[68]

The use of canned sieved vegetables and fruit for children has increased at a rapid rate in the last few years.[90] In spite of the most careful methods of processing, partial destruction of vitamin C is unavoidable. A great deal of variation in this occurs, depending on the type of food, freshness and method of processing, but in general it has been shown that the loss of vitamin C is slightly greater for purées than for the corresponding canned whole vegetables. As a rule these products cannot be classed as potent antiscorbutic foods, although they may contribute materially to the diet because of the quantity consumed.

Milk is the most nearly perfect and the least dispensable food. Nevertheless, the vitamin C content of commercial milk, raw or pasteurized, is not dependable and should never be relied on to supply the requirements. The use of the titration method has led to a better understanding of those factors which may influence the vitamin C content of milk, such as aging, pasteurization and handling. Judging from a large number of determinations, both biologic and chemical, one may expect from 2 to 2.5 mg. per hundred cubic centimeters of ascorbic acid in fresh raw milk.[91] Even when the milk is cold this value slowly decreases, until a loss of from 20 to 30 per cent may occur in twenty-four hours. Sunlight or traces of copper accelerate this change.[92] Pasteurization by the widely used holding method, unless unusual precautions are observed, results in a loss of from 30 to 60 per cent. However, pasteurization by the short time high temperature process with absence of copper leads to slight inactivation.[93] Loss of vitamin C activity due to pasteurization, aging, reheating and diluting, such as usually occurs in preparing a formula for babies, results in a formula of very low antiscorbutic value.[15]

Although Hess[94] found that a pint of milk a day prevented infantile scurvy, the commercial milk of today, which contains from 0.3 to 1 mg. per hundred cubic centimeters, is a rather poor source of vitamin C. The 5 mg. of ascorbic acid represented by a pint of average commercial milk is far below that recommended for optimum nutrition. This fact has led to the general use of orange juice, tomato juice or potent antiscorbutic substances as a supplement to the infant diet. A breast-fed infant of a normally nourished mother receives from 20 to 40 mg. of ascorbic acid daily from the day of birth, because human milk is from four to six times richer in vitamin C than cow's or goat's milk.[95] The implication is strong that vitamin C should be a constituent of the infant's diet at a very early age.

The ascorbic acid value of canned or dried milk[2] depends primarily on the method by which the milk is prepared or handled. Commercially evaporated milk which has been sterilized at a high temperature is almost free from vitamin C, while sweetened condensed milk which has been evaporated in vacuum at lower temperatures retains a proportion of vitamin C comparable to that of pasteurized milk. Several investigators have reported good conservation in dried milk.[68] However, most commercial preparations are practically free from vitamin C.[15]

The vitamin C concentrations of individual foods are summarized in the accompanying table. Most of the analyses reported were on fresh material. It is difficult to estimate values for cooked or processed food because of the lack of uniformity of methods and treatment. Lower vitamin C values than those given must be expected because of immaturity, lack of freshness, poor preservation, long storage or results of processing. The figures given are estimates derived after consideration of the available data,[96] including the results of many unpublished analyses from my own laboratory, and represent my judgment of the expected value of the raw edible portions under good market conditions. The value when the food is ready for serving will depend on the method of preparation. A recent United States Department of Agriculture bulletin[4] contains fuller details of the vitamin C contents of foods and also references to the literature.

90. Fellers, C. A.: Vitamin Content of Important Food in the Child's Diet, Am. J. Pub. Health **25:** 1340 (Dec.) 1935. Hanning, Flora: Comparison of the Biological and Chemical Method for the Determination of Vitamin C in Canned Strained Vegetables and a Study of Its Variation from Year to Year, J. Nutrition **12:** 405 (Oct.) 1936.

91. Rasmussen, Russel, and Guerrant, N. B.: The Effect of Breed Characteristics and Stage of Lactation on the Vitamin C (Ascorbic Acid) Content of Cow's Milk, J. Nutrition **11:** 425 (May) 1936. Riddell, W. H.; Whitnah, C. H.; Hughes, J. S., and Leinhardt, H. F.: Influence of the Ration on the Vitamin C Content of Milk, J. Nutrition **11:** 47 (Jan.) 1936. King and Waugh.[93]

92. Kon, S. K., and Watson, M. B.: The Effect of Light on the Vitamin C of Milk, Biochem. J. **30:** 2273 (Dec.) 1936. King.[23]

93. King, C. G., and Waugh, W. A.: Effect of Pasteurization on the Vitamin C Content of Milk, J. Dairy Sc. **17:** 489, 1934. Schwartze, E. W.; Murphy, F. J., and Hann, R. M.: Studies on the Destruction of Vitamin C in the Boiling of Milk, J. Nutrition **2:** 325 (March) 1930.

94. Hess cited by Sherman.[83]

95. Selleg, Ina, and King, C. G.: The Vitamin C Content of Human Milk and Its Variation with Diet, J. Nutrition **11:** 599 (June) 1936.

96. Daniel and Munsell.[4] Fellers.[68] Lack of space prevents reference to many of the papers considered.

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Council on Physical Therapy

THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING ARTICLE. HOWARD A. CARTER, Secretary.

AIR FILTRATION

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By air filtration is implied the removal of impurities, usually in the form of dust, from the air. The benefits derived from such treatment of the air are of great importance in industry as well as in the control of many respiratory diseases.

It can be stated that no air is free from dust. Dust comes from almost every process in which there is disintegration of materials and is thrown into the air by any method that will disturb the dust. Once the particles are in the air, they will remain suspended for varying periods of time, from a few seconds to years, depending on their size and density. Particles of dust differ in size from those which can be seen only by an ultramicroscope to those which are easily discerned by the naked eye, particles 10 microns in size or larger. However, the particles of most concern in their effect on the human body are those from 0.5 to 100 microns in size.

The concentration of dust particles in the air varies greatly, depending on the conditions operative in the locality where samples are taken. In country air which is comparatively clean, especially after a rain, the particles may be as low as a few thousand per cubic foot

of air, whereas city air will contain from five hundred thousand to two or three million particles per cubic foot. In heavy industrial centers the contamination has run as high as twenty million particles per cubic foot. Recent studies bear out previous observations of air pollution in both urban and rural areas.[1] In many industries the dust level is tremendous.

The normal concentration of permanent dust in the air is not of much concern, as it actually serves a useful purpose in reflecting light and forming nuclei for rain drops. There are, however, great objections to certain kinds of dust and to their heavy concentrations. In addition to the economic loss due to dust, the effect either direct or indirect on health is often of vital importance.[2] If the concentration is of sufficient magnitude, ultraviolet rays may be shut off.[3] Dust as nuclei for fine droplets of water may form fog in heavy industrial areas.

The direct effect of dusts on health depends to a large extent on their chemical composition and the size of the particles. In many industries dusts and fumes are liberated in sufficient quantities to be injurious to the health of the workers. Many such dusts are direct poisons, as arsenic, lead, mercury, manganese and cadmium. Lead poisoning is a classic example of a disease due to such an occupational hazard. Inhalation of other solid and gaseous ingredients of city air, such as carbon and sulfur fumes, irritates the mucous membranes of the nose, throat and lungs, producing discomfort, and in some instances it may cause injury to health.[4] In addition, the inhalation over long periods of fine inorganic dusts, such as silicates, iron, carbon and asbestos, leads to the fibroid condition of the lungs known as pneumoconiosis. These particles are probably smaller than 1 micron and when lodged in the alveoli of the lung produce a low grade inflammatory reaction and the appearance of dust carrying phagocytes. Passing into the lymphatics, the dust cells tend to migrate along the lymphatics to the hilar nodes. If present in excessive amounts, they block lymph flow, with resulting localized lymphoid hyperplasia and fibrosis.[5]

In persons who are sensitized to pollens, inhalation of these air impurities precipitates symptoms of hay fever and pollen asthma. The concentration of pollen in the air varies greatly in different localities and is often enormous. In Chicago, for example, it has been shown that hundreds of tons of ragweed pollen are liberated each season.[6]

Many mechanical devices have been built for removing dusts from the air. However, because of the large variety of dusts, their difference in size and chemical composition and the varying conditions under which they are found, there is no single filtration method which is applicable to all.

The main object is to remove as nearly 100 per cent of the dust as is possible. To this end Rowley[7] has laid down a group of fundamental requirements for air filtering devices, namely:

1. High efficiency, or dust arresting power.
2. Low resistance to the flow of air through the filter.
3. High dust-holding capacity, or long life in service.
4. Economy in first cost and upkeep.
5. Freedom from odors.
6. Fire resistance.
7. Uniform efficiency over a wide range of air temperature.
8. Low moisture absorption.

Obviously these requirements must be modified to fit certain types of air cleaning, such as the water spray.

Air cleansing may be accomplished in numerous ways. In general the methods can be roughly grouped into five main divisions: air washers (water sprays), dry filters, viscous coated filters, electrical precipitators and dynamic precipitators.

The results obtained from any specific type of filtering method depend on specific properties of the filtering device and the operating conditions under which it is used and will vary over a wide range. Each method has a definite field of usefulness and when used within its own limitations attains its maximum efficiency.

In general it may be stated that dusts of small size which are harmful to health require filtration of the highest efficiency under the most variable conditions. In industry, the dynamic and electrical precipitators are perhaps the most efficient for the removal of the smaller particles of dust, whereas for home and hospital use dry filters are most efficient.

The air washer for the removal of dust and pollen from air does not have as high a degree of efficiency as other methods. Mechanically it is impossible to remove all fine dust particles from a stream of air with an air washer. Bubbling air through a volume of water at a slow rate, particularly if the water is greatly agitated by mechanical means, gives a higher degree of efficiency in dust removal than the air washer. The greatest field of usefulness of the air washer is as a primary cleaner in a system in which there is a secondary filter of greater efficiency. In this capacity it will remove the larger particles and thus give a longer life to the secondary filter in addition to maintaining or increasing the humidity.

Dry filters are made from felt, closely woven cloth, cotton mats and cellulose material (paper type). A filter of this type is spread on a frame, usually in a fluted fashion to give a large filtering surface to allow a slow seepage of air. Modern developments in this type of filtering medium permit large volumes of air to be passed through the filter without sacrificing efficiency. It is apparent that this type of filtering material is superior to water cleaning as well as viscous coated filters for the removal of dusts and pollens injurious to health. Such filters are well adapted for installation in hospitals and homes where filtration is required. Their efficiency is at its maximum when the filter is new. When properly cared for under ordinary operating conditions, the loss in efficiency of dry filters is very slight.

Viscous coated filters are made of numerous types of materials such as spun glass, metal wool or fibrous material, which are usually packed loosely in a frame or so arranged that the air is deflected from surface to surface. The material is coated with a thick viscid oil. The retention of dust is due to the fact that it sticks

1. Atmospheric Contamination, editorial, J. A. M. A. **110:** 1839 (May 28) 1938.
2. Bloomfield, J. J.: Outdoor Life **25:** 457, 1928
3. Schrader, J. H.; Coblentz, M., and Korff, F. A.: Am. J. Pub. Health. **19:** 7, 1929.
4. Report of the Committee on Public Health of the New York Academy of Medicine, Bull. New York Acad. Med. **7:** 751, 1931. Yaglou, C. P.: Heating, Piping and Air Conditioning, 1931, p. 57; Physical and Physiologic Principles of Air Conditioning, J. A. M. A. **108:** 1708 (May 15) 1937; ibid. **109:** 945 (Sept. 18) 1937.
5. Funk, Elmer H.: Oxford Monographs on Diagnosis and Treatment **5:** 255, 1936.
6. Koessler, K. K., and Durham, O. C.: A System for an Intensive Pollen Survey, J. A. M. A. **86:** 1204 (April 17) 1926.
7. Rowley, Frank B.: Univ. Illinois Bull. **34:** 45 (Oct.) 1936.

to the oily surfaces and not that particles cannot pass through the openings. This type of filter has its lowest efficiency for dust arrestment when new, but as the filter fills with dust the efficiency increases.[7]

Electrical precipitators have lately been advocated for use in the removal of dust and pollen from the air. They maintain a high degree of efficiency for dust removal. The operating principle is not new in industry, where it is known as the Cottrell method. It consists of suspending a wire at a high potential below a series of plates which are oppositely charged. The dust particles are charged by the high potential wire and in passing over the plates are electrically attracted to them and stick there. This method is efficient for particles smaller than 0.5 micron. Its disadvantages for home and hospital use are that it may liberate ozone, which at times may produce secondary effects, and it requires constant operation to maintain its efficiency. If the unit is shut down, the particles which have become adherent to the plates lose their charge and may fall to the bottom of the ducts, and when operation of the unit is resumed these may be blown out in a large volume. The electrical filtering device therefore requires a supplementary filter when used in homes or hospitals. A filter to be used in homes or hospitals should be as foolproof as possible.

Dynamic precipitators usually combine an exhauster and dust collector in a single unit. There is a primary and secondary air passage and a turbine-like impeller composed of a large number of carefully calculated hyperboloid blades. The dust laden air is drawn into the unit by forces created by the rotating impeller; then the dust is separated and the cleaned air discharged. Dust drawn off by the impeller is directed through the secondary air circuit and collected in a hopper or passed outdoors. The dynamic precipitator has a very high degree of efficiency for dust removal as the result of the magnitude of the centrifugal and dynamic forces imparted to the dust particles by the impeller.

Within the past ten years, filtration of air for the removal of particulate matter has received a great deal of attention from the medical profession.[8] This has been particularly true in the field of allergy. Its usefulness in the relief of symptoms of hay fever and pollen asthma and in other inhalant allergies as well as its value as an aid in diagnosis has been amply demonstrated.[9] A brief survey of its value as shown by numerous workers may be summarized as follows: In uncomplicated hay fever, residence of the patient in adequately filtered air will prevent the onset of symptoms due to sensitivity to pollens. Symptoms appear as soon as the person is exposed to pollen laden air. Persons experiencing symptoms due to pollen are relieved on entering a room with adequately filtered air, the length of time required for such relief depending on the severity of symptoms on entering. In a large series of observations, the average time required for maximum relief was found to be 1.2 hours.[10] Residence in dust and pollen free air does not increase a person's resistance to pollen or dust, nor is it a cure for pollinosis or dust sensitivity.

Pollen asthma likewise will be relieved by residence in adequately filtered air, the length of time required for such relief varying greatly with the severity of the asthma and the duration of the attack. This time may vary from a few hours to several days or even weeks.[11] The subjective symptoms clear up more rapidly than do the objective symptoms. Persons who have pollen asthma remain free as long as they remain in filtered air, with certain exceptions. As has been shown,[12] atmospheric changes of wide amplitude may precipitate severe symptoms in persons with pollen asthma confined in adequately filtered air. However, the patients must first have been exposed to pollen. Other factors of air conditioning such as controlled humidity and temperature play a definite role in the relief of pollen asthma. It has been observed that the rapidity with which persons who have pollen asthma are relieved is greater under conditions of low humidity and relatively constant temperature in pollen free atmosphere than when the temperature and humidity are not controlled.[13] In such controlled atmospheres, attacks of asthma precipitated by storms were apparently delayed from six to eight hours and were less severe than those observed when humidity and temperature were not controlled.[13]

Residence in adequately filtered air is a procedure of great help in the diagnosis of allergic conditions. The effect of dusts, pollens and other inhalant factors usually may be ruled out in a few days by this method.

In other respiratory conditions which are definitely attributed to the effect of dust such as pneumoconiosis, the use of air filtration for removal of dusts is now a recognized preventive measure. Many industries, realizing the benefits derived by the employees from such treatment of the air, have installed devices for the removal of dust.[14]

Air conditioning is recognized as most essential in many manufacturing processes, as for example in the production of rayon, photographic film, capsules, candy,

8. Taylor, T. A., and Taylor, W. H.: Anesth. & Analg. **13:** 22 (Jan.-Feb.) 1934. Linke, F.: Ztschr. f. d. ges. Krankenhausw., Oct. 30, 1934, p. 509. Beach, B. S.: Scient. Am. **157:** 152 (Sept.) 1937.

9. This work has been described in the articles listed in footnote 11 and also in the following:
Storm van Leeuwen, W.: Proc. Roy. Soc., Section of Therapeutics and Pharmacology, part 3, **17:** 19 (April) 1924.
Storm van Leeuwen, W.: München. med. Wchnschr. **77:** 726, 1930.
Leopold, S. S., and Leopold, C. S.: Bronchial Asthma and Allied Allergic Disorders, J. A. M. A. **84:** 731 (March 7) 1925.
Cohen, M. B.: M. J. & Rec. **123:** 322 (March 3) 1926.
Peshkin, M. M., and Beck, I.: J. Lab. & Clin. Med. **15:** 643 (April) 1930.
Storm van Leeuwen, W., ibid. **16:** 442 (Feb.) 1931.
Gay, L. N.: The Treatment of Hay Fever and Pollen Asthma by Air-Conditioned Atmosphere, J. A. M. A. **100:** 1382 (May 6) 1933.
Griebel, C. R.: Ztschr. f. Laryng., Rhin. & Otol. **24:** 207, 1933.
Rowe, A. H.: M. J. & Rec. **138:** 345 (Nov. 15) 1933.
Vaughan, W. T., and Cooley, L. E.: J. Allergy **5:** 37 (Nov.) 1933.
Kahn, I. S., and Grothaus, E. H., ibid. **5:** 45 (Nov.) 1933.
Kendal, T. A., and Weidner, G.: Heating, Piping and Air Conditioning, February 1934, p. 75.
Davies, C.: M. J. & Rec. **139:** 543 (May 16) 1934.
Habetin, P.: Wien. klin. Wchnschr. **47:** 651 (May 25) 1934.
Criep, L. H., and Green, M. A.: J. Allergy **7:** 120 (Jan.) 1936.
Criep, L. H.: Mod. Hosp. **46:** 82 (June) 1936.
von Neergaard, K.: Balneolage **3:** 386 (Aug.) 1936.
von Neergaard, K.: Schweiz. med. Wchnschr. **66:** 837 (Aug. 29) 1936.
Welker, W. H.: Univ. Illinois Bull. **34:** 15 (Oct.) 1936.
Fraenkel, E. M.: Proc. Roy. Soc. Med. **30:** 1547 (Oct.) 1937.
Voss, O.: Beitr. z. Klin. d. Tuberk. **89:** 311, 1937.

10. Rappaport, B. Z.; Nelson, Tell, and Welker, W. H.: Effect of Air Filtration in Hay Fever and Pollen Asthma, J. A. M. A. **98:** 1861 (May 28) 1932.

11. Reported in the following articles:
Cohen, M. B.: Clin. Med. & Surg. **34:** 276 (April) 1927; J. Lab. & Clin. Med. **13:** 59 (Oct.) 1927, 963 (July) 1928.
Kahn, I. S., in discussion on Cohen: J. Lab. & Clin. Med. **13:** 963 (July) 1928.
Rappaport, Nelson and Welker, footnotes 10 and 12.
Nelson, Tell; Rappaport, B. Z.; Canar, A. G., and Welker, W. H.: Heating, Piping and Air Conditioning **6:** 329 (Aug.) 1934.
Rappaport, Nelson and Welker.[13]
Nelson, Tell; Rappaport, B. Z.; Canar, A. G., and Welker, W. H.: Am. Gas A. Month. **17:** 6 (Jan.) 1935.
Nelson, Tell; Rappaport, B. Z., and Welker, W. H.: Chicago Purchasor **13:** 28 (June) 1935.
Ward, C. E.: Proc. Staff Meet., Mayo Clin. **11:** 609 (Sept. 23) 1936.
Trasoff, Abraham, and Blumstein, George: J. Lab. & Clin. Med. **22:** 147 (Nov.) 1936.

12. Nelson, Tell; Rappaport, B. Z., and Welker, W. H.: The Effect of Air Filtration in Hay Fever and Pollen Asthma, J. A. M. A. **100:** 1385 (May 6) 1932.

13. Rappaport, B. Z.; Nelson, Tell, and Welker, W. H.: J. Allergy **6:** 111 (Jan.) 1935.

14. Hatch, Theodore; Warren, Henry, and Kelley, G. S.: J. Indust. Hyg. **14:** 246 (Sept.) 1932. Hatch, Theodore; Fehnel, J. W.; Warren, Henry, and Kelley, G. S., ibid. **15:** 41 (Jan.) 1933. Hatch, Theodore: J. Indust. Hyg. & Toxicol. **18:** 595 (Nov.) 1936. Price, C. W.: Proc. Roy. Soc. Med. **30:** 1544 (Oct.) 1937.

chemicals, flour, textiles, linoleum, watches, safety glass, powdered milk, tobacco products, fine printing and lithography, and in many laboratories. The control of air-borne fungi and molds in such industries as brewing has been greatly aided by the use of air filtration. In most of these industries, air cleanliness is of equal importance to the control of humidity and temperature and forms a most essential part of the air conditioning mechanism.

The progress made in the field of air filtration within the past few years has been a great help in both industry and medicine. The deleterious effect of dusts on health is now a well recognized fact and the removal of dust particles has definitely been established as beneficial. Further application of the principles of air filtration to other fields of medicine and industry will result in greater perfection of filtration appliances with a higher degree of efficiency.

636 Church Street, Evanston, Ill.

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

PAUL NICHOLAS LEECH, Secretary.

ANTIMENINGOCOCCIC SERUM (See New and Nonofficial Remedies, 1937, p. 395).

The Gilliland Laboratories, Inc., Marietta, Pa.

Antimeningococcic Serum, Concentrated and Refined—Gilliland.—Serum which has been refined and the antibodies so concentrated that 10 cc. is equal to at least 40 cc. of the whole (unrefined) serum. The concentrated serum is equivalent in activity to several times the quantity of unconcentrated serum. The concentrated serum is desirable for intravenous administration, since much of the inert protein has been removed, and for intraspinal administration where often it is possible to withdraw only small amounts of spinal fluid, as in children. The serum is tested for its precipitin and agglutinin content in mice and is standardized according to the requirements of the National Institute of Health. Marketed in packages of one 10 cc. double end vial and in packages of one 10 cc. double end vial with sterile intraspinal needle and improved gravity injecting outfit. A vial of a 1:10 dilution of this serum is included with each package for determining the sensitivity of the patient.

Dosage.—The usual intraspinal dose for adults and children is 10 to 20 cc., repeated every twenty-four hours until at least two successive specimens of fluid show no organisms by bacteriologic examination. It is necessary to exercise more than ordinary care in removing fluid and injecting serum in babies. In addition to the intraspinal dose, 5 cc. for children and 20 cc. for adults may be administered intravenously in very early cases or in those cases accompanied by frank meningococcemia as demonstrated by positive blood cultures.

NICOTINIC ACID (See THE JOURNAL, July 2, 1938, p. 27).

Tablets Nicotinic Acid, 50 mg.
Prepared by John Wyeth & Brother, Inc., Philadelphia.
Tablets Nicotinic Acid, 100 mg.
Prepared by John Wyeth & Brother, Inc., Philadelphia.

SULFANILAMIDE-ABBOTT (See THE JOURNAL, March 12, 1938, p. 815).

The following dosage form has been accepted:

Sulfanilamide-Abbott, 1 Gm. Ampoules (Crystals).

McKESSON'S COD LIVER OIL CONCENTRATE IN OIL, 6 CC.—A concentrate of the nonsaponifiable fraction of cod liver oil adjusted to a potency, by dilution with corn oil, of 58,800 units (U. S. P.) of vitamin A per gram and not less than 5,880 units (U. S. P.) of vitamin D per gram.

Actions and Uses.—It possesses the therapeutic properties recognized for the vitamins present in cod liver oil.

Dosage.—Prophylactic, for infants and children 6 to 9 drops daily, or as prescribed by the physician.

Manufactured by the International Vitamin Corporation, New York (McKesson & Robbins, Inc., Bridgeport, Conn., distributor). The vitamin D concentrate used is made under U. S. patent No. 1,690,091.

ESTRONE (THEELIN) (See THE JOURNAL, Aug. 27, 1938, p. 784).

Estrone-Abbott.—A brand of estrone (theelin)-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill., by license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951). No U. S. trademark.

Ampoules Estrone, 0.1 mg. in oil, 1 cc.: Each cubic centimeter contains estrone 0.1 mg. (1,000 international units) in sesame oil.

Ampoules Estrone, 0.2 mg. in oil, 1 cc.: Each cubic centimeter contains estrone 0.2 mg. (2,000 international units) in sesame oil.

Ampoules Estrone, 1 mg. in oil, 1 cc.: Each cubic centimeter contains estrone 1 mg. (10,000 international units) in sesame oil.

Vaginal Suppositories Estrone, 0.02 mg.: Each suppository contains estrone 0.02 mg. (200 international units) in a glycerogelatin base.

Vaginal Suppositories Estrone, 0.2 mg.: Each suppository contains 0.2 mg. (2,000 international units) in a glycerogelatin base.

ESTRIOL (THEELOL) (See THE JOURNAL, Aug. 27, 1938, p. 784).

Estriol-Abbott.—A brand of estriol (theelol)-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill., by license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951). No U. S. trademark.

Capsules Estriol 0.06 mg.: Each capsule contains estriol 0.06 mg. diluted with milk sugar.

Capsules Estriol 0.12 mg.: Each capsule contains estriol 0.12 mg. diluted with milk sugar.

DIGITALIS (See New and Nonofficial Remedies, 1938, p. 186).

Pulvoids Digitalis Folium, ½ grain: Each pulvoid (compressed powder in tablet form) represents one-third cat unit.
Prepared by the Drug Products Company, Inc., Long Island City, N. Y.

Pulvoids Digitalis Folium, ¾ grain: Each pulvoid (compressed powder in tablet form) represents one-half cat unit.
Prepared by the Drug Products Company, Inc., Long Island City, N. Y.

Pulvoids Digitalis Folium, 1½ grains: Each pulvoid (compressed powder in tablet form) represents 1 cat unit.
Prepared by the Drug Products Company, Inc., Long Island City, N. Y.

DIPHTHERIA TOXOID, ALUM PRECIPITATED (REFINED) (See New and Nonofficial Remedies, 1938, p. 417).

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

Diphtheria Toxoid, Alum Precipitated (Refined).—Also marketed in packages of one 10 cc. vial (ten immunizations).

PROPADRINE HYDROCHLORIDE-SHARP & DOHME (See New and Nonofficial Remedies, 1938, p. 237).

The following dosage forms have been accepted:

Propadrine Hydrochloride Capsules, ¾ grain.

Propadrine Hydrochloride Solution 3%: An aqueous solution containing 3 per cent propadrine hydrochloride and 0.5 per cent chlorbutanol as a preservative.

TETANUS TOXOID, ALUM PRECIPITATED (See New and Nonofficial Remedies, 1938, p. 424).

E. R. Squibb & Sons, New York.

Refined Tetanus Toxoid, Alum Precipitated-Squibb.—Marketed in packages of two 1 cc. vials (one immunization treatment). The preparation contains merthiolate 1:10,000.

CEVITAMIC ACID (See New and Nonofficial Remedies, 1938, p. 480).

Cevitamic Acid-Abbott.—A brand of cevitamic acid-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago. No U. S. patent or trademark.

Tablets Cevitamic Acid-Abbott, 0.025 Gm.
Tablets Cevitamic Acid-Abbott, 0.1 Gm.

EPHEDRINE ANHYDROUS (See New and Nonofficial Remedies, 1938, p. 225).

Ephedrine Alkaloid Anhydrous-Gane and Ingram.—A brand of ephedrine anhydrous-N. N. R.

Manufactured by Gane's Chemical Works, Inc., New York (Gane & Ingram, Inc., New York, distributor). No U. S. patent or trademark.

EPHEDRINE HEMIHYDRATE (See New and Nonofficial Remedies, 1938, p. 226).

Ephedrine Alkaloid Hemihydrate-Gane and Ingram.—A brand of ephedrine hemihydrate-N. N. R.

Manufactured by Gane's Chemical Works, Inc., New York (Gane & Ingram, Inc., New York, distributor). No U. S. patent or trademark.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, OCTOBER 1, 1938

THE FOOD, DRUG AND COSMETIC ACT BEGINS TO FUNCTION

The month of July witnessed the beginning of enforcement of the Federal Food, Drug and Cosmetic Act of 1938. While the majority of the provisions of the act will not become effective until next June, dangerous drugs and dangerous cosmetics are immediately subject to the new law. Moreover, the provisions concerning the introduction of new drugs are also in effect.

The American Medical Association took an active part in procuring the enactment of the Federal Food and Drugs Act of 1906, which in its final form was obviously inadequate to accomplish the purposes for which it was intended. The Association has cooperated and is cooperating to the extent of its ability in bringing about the enforcement of that act and of its several amendments, and through THE JOURNAL, the Bureau of Investigation and its Councils has endeavored to keep the public and the profession informed about many harmful, deleterious or unscientific preparations. The Association proposes to follow the same policy with respect to the new act.

Although the present act is not nearly perfect, it has removed certain restrictions; the government may now proceed to act against products not previously within the purview of the law. Many years ago the Bureau of Investigation published a report on irrational or other dangerous cosmetic preparations for dyeing eyebrows and eyelashes. One particularly (Lash Lure) was reported to contain the dangerous paraphenylenediamine mixture. THE JOURNAL called attention to cases of blindness which followed the use of this preparation by some persons. The Food, Drug and Cosmetic Administration of the United States Department of Agriculture in its report for the month of July states that it has proceeded against "Lash Lure" and other similar preparations. The manufacturer of "Lash Lure" has notified the administration through its attorney that it was ceasing shipments immediately.

Physicians not long ago were urged to the use of a product called Causalin. THE JOURNAL pointed out its deficiencies and more recently a critical report[1] was issued by the Council on Pharmacy and Chemistry. In this report the Council indicated that Causalin was apparently a mixture containing an aminopyrine preparation and a derivative having chemical resemblance to cinchophen. Now the firm has been cited by the government because, the government alleges, the subsidiary label statement "Aminodimethyl-pyrazolon-Quinoline-sulphonate" was a false representation of the composition of the medicine, since other significant ingredients were present. The government alleges that the product, a pain-relieving preparation, is dangerous to health when used in dosages or with the frequency prescribed, recommended and suggested in the labeling.

Of much interest to physicians is the recent ruling of the Food and Drug Administration on sulfanilamide. Under the dangerous drugs provision of the new Food, Drug, and Cosmetic Act sulfanilamide is prohibited from being sold to the public in "patent medicines" so far as:

> It is the consensus of qualified experts that sulfanilamide is a valuable aid in the treatment of several serious disease conditions when the dosage is properly adjusted to the requirement of the individual patient and frequency of dosage and duration of treatment are intelligently and expertly directed. It is further the consensus of such experts that, when used under other conditions, it is a dangerous drug, capable of causing serious injury and even death.
>
> In the light of these facts, careful consideration has been given to the status of sulfanilamide under the provisions of the Food, Drug and Cosmetic Act which deals with traffic in dangerous drugs.
>
> Sulfanilamide and drug preparations containing sulfanilamide or related compounds for indiscriminate use by the general public, in a manner which constitutes a serious danger to health, are, when found in interstate commerce, actionable, in the opinion of the Food and Drug Administration, under section 502 (j) of the Federal Food, Drug and Cosmetic Act, which section of the law is now in effect.

Similar ruling has been made for aminopyrine, for cinchophen and for neocinchophen.

Another item in the report of the Food and Drug Administration for the month of July refers to an investigation of a number of food products. Among them was a consignment of curry powder heavily contaminated with lead. Among the allegations made was that against 577 cans of a malted milk food drink containing little or no malted milk; 19,062 pounds of a so-called cocoa containing at least 12 per cent added vegetable gum; 426 packages of butter cookies containing little or no butter; 19 gallons of so-called lemon juice, found to be an imitation; 150 gallons of refined soy bean oil which was found to be 90 per cent mineral oil; a sizable quantity of horseradish made up entirely of parsnips flavored with mustard oil and vinegar, and 104 sacks of caraway seed from which nearly all the essential flavoring oil had been distilled.

The Food and Drug Administration continued its campaign of confiscation against unsterile gauze bandages and absorbent cotton, of which there seems to be

1. Causalin (Causyth) Not Acceptable for N. N. R., J. A. M. A. **109**: 506 (Aug. 14) 1937.

a profuse amount on the market. Among other confiscations were sixty bottles of milk of magnesia with cascara and sixty-three bottles of milk of magnesia with vanilla and sugar, both failing to conform to their label claims of composition.

The Federal Trade Commission also has serious responsibilities in the regulation of advertising to the public. Recently it issued a release in which it is indicated that the U. S. District Court of Chicago has issued an order temporarily restraining the Hartman chain of drug stores from disseminating in any manner false advertisements concerning a weight reducing compound. The bill of complaint alleges that the defendant has falsely advertised the product for the purpose of inducing, or as a product which is likely to induce, its purchase as a weight reducer. According to the complaint the advertisement is false. Not only is the product not widely prescribed by practicing physicians, but also the advertisement fails to reveal that the use of this product under the conditions recommended may be injurious to the health of the user by causing loss or serious impairment of eyesight. It was brought out that the active ingredient in the drug is known as dinitrocresol. This is essentially similar in action to dinitrophenol. An affidavit by Dr. Harry Gradle states that he treated a Chicago woman suffering from a cataract of each eye following the use of the nostrum. THE JOURNAL and the Council on Pharmacy and Chemistry have frequently warned against the use of the nitrophenol type of weight reducing preparations.

The medical profession will follow with interest the further work of the Food and Drug Administration and the Federal Trade Commission since they have been fortified with new laws to combat deception. Some time may elapse before the courts will pass judgment on the new laws; until this is done their exact status will not be known. The medical profession will always be found solidly with the government in its protection of the public against the exploiters of impure or harmful foods, drugs and cosmetics.

PROTRUDED INTERVERTEBRAL DISK, BACK PAIN AND SCIATICA

Medical periodicals of the past few years contain a number of contributions dealing with the rupture of the intervertebral disk and its herniation into the spinal canal as a cause of intractable back pain and sciatica. The center of interest for the student of these conditions seems to have shifted from spondylolisthesis to the rupture of the nucleus pulposus. The exact knowledge of the anatomy and embryology of this long neglected structure dates back to the anatomic studies of von Luschka (1858). A correct clinical or pathologic approach to the subject of the intervertebral disk, however, is a recent contribution, the result of the accurate and painstaking necropsy studies of the Dresden pathologist Schmorl.

Briefly the intervertebral disk consists of an outer dense fibrocartilage firmly attached to the adjacent vertebrae and forming a strong but elastic ring, annulus fibrosus or lamellosus, acting as an envelop for the interior semifluid mass of fibrogelatinous pulpy center, the nucleus pulposus. The firm fluid cushion or shock absorber is subject, as pointed out by Keyes and Compere,[1] to the laws of fluids. It is incompressible and confined to its normal shape and position by the strong and elastic annulus fibrosus. The amount of compression of the intervertebral disk will therefore depend on the elasticity and strength of the annulus fibrosus. The incompressibility of the nucleus pulposus lends to it the function of transmitting the static and muscular forces from one vertebra to the next and establishes it as the axis of motion on which each vertebral body must work.

Schmorl found in his necropsy studies of the spine that the intervertebral disk is often involved in pathologic changes, the most common being prolapse (38 per cent) of the nucleus pulposus into the spongiosa of the adjacent vertebra, leading later to the formation in the involved vertebra of the so-called Schmorl nodules. He discovered further that in about 15 per cent there were small posterior prolapses of the nucleus pulposus beneath the posterior longitudinal ligament but concluded that they rarely, if ever, produced clinical symptoms. He advanced the concept of the rupture of the nucleus pulposus as the starting point for a number of pathologic changes in the spine, the rupture being facilitated or caused by the degenerative changes in the annulus fibrosus, with mild trauma as a second factor.

The earliest clinical report of this condition was that of Goldthwaite, who reported a case of sciatica and paraplegia due to a posterior herniation of the intervertebral disk at the lumbosacral junction. He suggested that such displacements might be the cause of many cases of sciatica, lumbago and back strain. A similar case was reported by Middleton and Teacher of England, but both observations attracted little interest. In the next decade and a half, a number of neurosurgeons, among them Elsberg, Stookey, Bucy, Adson and Dandy, reported cases of enchondroma developing from the intervertebral disk and causing spinal cord compression. In 1934 Mixter and Barr [2] reported from the Massachusetts General Hospital a series of nineteen cases of rupture of the disk, establishing it as a clinical entity and a cause of intractable back pain and sciatica. In 1935 Mixter and Ayer [3] added observations on fifteen more cases. In THE JOURNAL, Love and Walsh [4] have reported 100 cases in which the protruded inter-

1. Keyes, D. C., and Compere, E. L.: The Normal and Pathological Physiology of the Nucleus Pulposus of the Intervertebral Disk, J. Bone & Joint Surg. **14**: 897 (Oct.) 1932.

2. Mixter, W. J., and Barr, J. S.: Rupture of the Intervertebral Disk with Involvement of the Spinal Canal, New England J. Med. **211**: 210 (Aug. 2) 1934.

3. Mixter, W. J., and Ayer, J. B.: Herniation of Rupture of the Intervertebral Disk into the Spinal Canal, New England J. Med. **213**: 385 (Aug. 29) 1935.

4. Love, J. G., and Walsh, M. N.: Protruded Intervertebral Disks, J. A. M. A. **111**: 396 (July 30) 1938.

vertebral disk was removed at operation. It appeared that the enchondromas of the earlier reports were in reality prolapsed nuclear material impinging on the cord, cauda equina, nerve routes or posterior longitudinal ligament. The favorite location is the lower lumbar region, probably because it is subjected to the greatest mechanical stress in heavy lifting or pushing.

The clinical diagnosis of a protruding disk as the cause of sciatica is based, according to Love and Walsh, on a history of trauma to the back with persistent or recurrent low back and sciatic pain, with diminished or absent achilles reflex, and an increased total protein content of the cerebrospinal fluid. The diagnosis is confirmed and the protruded disk identified by fluoroscopic examination of the spinal canal after the subarachnoid injection of iodized oil through a lumbar puncture needle. If on examination of the movements of the opaque oil in the spinal canal a persistent defect characteristic of protruded disk is observed, and if a lesion located at that level could account for the patient's pain, surgical removal of the protruded portion of the disk is indicated. Barr [5] has reported that fifty-four patients of fifty-eight operated on were either well or markedly improved, and Love and Walsh state that there has not been a single recurrence in their series of 100 cases. The incidence of this entity is unknown. According to Barr, 90 or 95 per cent of the patients who have sciatica recover either spontaneously or after conservative treatment and do not need to be subjected to the highly technical and possibly dangerous examination with iodized oil. It is well, perhaps, to heed his admonition that there is some danger that too many patients will be subjected to examination with iodized oil or to radical exploratory surgery as a result of the untempered enthusiasm of certain men who assume that this entity is the cause of all sciatica.

Current Comment

ASCITIC FLUID TRANSFUSION

Davis and White [1] of the Department of Surgery, George Washington University School of Medicine, have reported recently that human ascitic fluid may be successfully substituted for whole blood in transfusion. Ascitic fluid has the advantage of low cost, as a constant source of supply is present in every hospital. The fluid is readily maintained in a sterile condition and does not deteriorate on storage. While their conclusions are based solely on experiments with transfusion in dogs, they see no reason why their results should not be equally applicable to man. Various substitutes for whole blood have been suggested and tried in transfusion. Gum-saline and gelatin-saline solutions were extensively used during the World War. More recent tests have been with hemoglobin Ringer's solution, or with whole blood or plasma obtained from the placenta, umbilical cord or cadaver. In their attempt to find a less objectionable substitute, the Washington surgeons withdrew peritoneal exudate from patients suffering from cardiac decompensation or portal cirrhosis. The fluids were filtered through gauze and stored without preservative at 5 C. for varying periods up to five months. Bacteriologic examinations made at intervals by the blood-agar plate method showed that the fluids were sterile. Compatibility tests with the blood of the prospective canine recipients were made before transfusion. The dogs weighed from 7 to 10 Kg. and were given pentobarbital sodium anesthesia. Shock was induced in these dogs by the gradual withdrawal of about 350 cc. of arterial blood. The average initial blood pressure (kymograph tracing), about 150 mm. of mercury, was reduced to about 55 mm. by this bleeding. About 500 cc. of ascitic fluid was warmed to 33 C. and allowed to flow into the femoral vein at the rate of 15 cc. per minute. As a result of this ascitic transfusion the carotid pressure was raised to 120. The animals survived indefinitely and did not show immediate or delayed transfusion toxicity. Albuminuria, glycosuria or hematuria was never observed. Whether or not retransfusion after an incubation period of from three to five weeks would produce retransfusion shock was not tested. The possibility of evaporating the ascitic fluid to dryness and redissolving before transfusion has not yet been tried.

EFFECT OF INSULIN IN VITRO

One of the most important of the unsolved problems in the biologic sciences is the mechanism of the action of insulin. The injection of insulin promotes the oxidation of carbohydrate but the exact mode of action of the hormone in stimulating these processes is not certain. The many physiologic variables present in the organism have made it extremely difficult to separate the processes involved in the action of insulin, even though the effects of the hormone have been rather completely postulated from work on the intact diabetic organism. Many efforts have been made to simulate the results of the activity of insulin by a large variety of in vitro experiments. The complete description of the mode of insulin action would no doubt greatly increase the amount of available information regarding carbohydrate metabolism and might perhaps also indicate how intimately the oxidation of fatty acids is related to the simultaneous combustion of carbohydrate. Past work has, however, yielded for the most part essentially negative results. The importance of the problem increases the significance of a recent article [1] describing an effect of insulin on oxidations in isolated muscle tissue. In a study of the respiration of minced pigeon breast muscle, in the Warburg apparatus, it has been demonstrated that the addition of insulin retards the decline in respiration, which under these conditions ordinarily begins from half an hour to an hour after the initiation of the experiments. The falling off in the respiration is also inhibited by the addition of citrate or certain compounds derived from citrate (succinate, fumarate) all of which have been postulated as inter-

5. Barr, J. S.: The Relationship of the Intervertebral Disk to Back Strain and Peripheral Pain (Sciatica), Surgery **4**: 1 (July) 1938.

1. Davis, H. A., and White, C. S.: Proc. Soc. Exper. Biol. & Med. **38**: 462 (May) 1938.

1. Krebs, H. A., and Eggleston, L. V.: Biochem. J. **32**: 913 (May) 1938.

mediates in the biologic oxidation of carbohydrates.[2] Particularly noteworthy is the fact that insulin has its greatest effect if added together with citrate and muscle extract, and it is therefore concluded that insulin acts as a catalyst in a "citric acid cycle".[2] The exact significance of these results cannot be determined until many more experimental data have become available. The observations are perhaps most noteworthy because of the finding of a positive effect for insulin. It should be pointed out, however, that the quantities of insulin required to demonstrate this in vitro action are approximately twenty times greater than the amounts required to produce an effect in the intact organism. Quite likely the entire mechanism of the action of insulin is not attributable to a single primary stimulation of the oxidation of carbohydrate. Nevertheless the results suggest the possibility of demonstrating in vitro other primary effects of insulin on carbohydrate metabolism.

2. Krebs, H. A.; Salvin, Ernest, and Johnson, W. A.: Biochem. J. 32:113 (Jan.) 1938.

Association News

ABSTRACT OF MINUTES OF MEETINGS OF BOARD OF TRUSTEES HELD IN CHICAGO, SEPT. 15-17, 1938

Meetings of the Board of Trustees were held on Thursday, Friday and Saturday of the week of the special session of the House of Delegates, and the following actions were taken:

ST. LOUIS SESSION

May 15-19, 1939, was the date set for the St. Louis session of the Association, and the nomination by the St. Louis Medical Society of Dr. Robert E. Schlueter as chairman of the Local Committee on Arrangements was confirmed.

APPOINTMENTS

Drs. George Blumer and Paul J. Hanzlik were reappointed on the Committee on Scientific Exhibit for a period of three years.

Drs. William P. Wherry, Paul Titus, John R. Neal, Charles B. Pinkham, S. S. Goldwater, Malcolm T. MacEachern, Donald Balfour and Alan M. Chesney and Rev. Alphonse M. Schwitalla were elected to constitute an Advisory Committee to the Council on Medical Education and Hospitals.

APPROPRIATIONS

Appropriations were made for special exhibits on anesthesia and fractures for the St. Louis session of the Association; for an investigation by the Council on Foods of the lead content of certain foods, particularly products used in infant feeding, and for the expansion of the public relations activities of the Association.

PUBLICATION OF BOOKS

Authorization was given for the printing of a limited edition of the manual for periodic health examinations to meet current needs, and for the development of a new manual. Permission also was granted for the reprinting in book form, in English and in Spanish, of the series of articles on vitamins which appeared in THE JOURNAL.

POSTPONEMENT OF CONFERENCE ON MEDICAL PATENTS

Because of preparations for conferences and meetings that were not previously contemplated, it has been difficult to carry out the plan of calling a conference on medical patents early in the fall. This matter will be given further consideration at the November meeting of the Board.

MISCELLANEOUS

Numerous other matters received consideration, and many of these will be acted on at a later date.

FORMER DELIBERATIONS

Appointments: The following appointments were made at the former meeting of the Board, and acceptances have been received:

Dr. Russell Haden to succeed Dr. L. R. Thompson as the Association's representative on the Division of Medical Sciences of the National Research Council for a period of three years.

Dr. Irvine McQuarrie to succeed Dr. Grover T. Powers on the Council on Foods.

Dr. Edmund V. Cowdry to succeed Dr. George W. Churchman on the Commission on Standardization of Biological Stains.

Drs. L. D. Bristol, A. J. Lanza and C. D. Selby as additional members of the Council on Industrial Health.

Dr. W. W. Bauer to serve on Joint Committee on Nursing Service.

Dr. Morris Fishbein to represent the Association on the Joint Committee to Investigate the Problems of Indexing and Abstracting Services in the Major Fields of Research proposed by the American Library Association.

Drs. Allen H. Bunce, Thomas S. Cullen and Roger I. Lee to constitute the Committee on Scientific Exhibit.

RADIO BROADCASTS

The fourth series of programs broadcast in dramatic form portraying fictitious but typical incidents of significance in relation to health by the American Medical Association and the National Broadcasting Company entitled "Your Health" will begin Wednesday, October 19, and run consecutively for thirty-six weeks. The program will be broadcast over the Blue network of the National Broadcasting Company each Wednesday at 2 p. m. eastern standard time (1 p. m. central standard time, 12 noon mountain time, 11 a. m. Pacific time).

These programs will be broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations and no revenue is derived from the programs. Therefore, local stations may or may not take the program, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

The program to be broadcast in the first group, together with their dates and their topics, are as follows:

October 19. What Is Health?
October 26. Growing Strong.
November 2. Seeing and Hearing Well.
November 9. Healthier Boys and Girls.

The following is a list of the stations connected with the Blue network of the National Broadcasting Company, but no assurance can be given as to how many of these stations will broadcast the program "Your Health":

Basic Blue Network

WJZ	New York	WEBR	Buffalo	KSO	Des Moines
WBZ	Boston	KDKA	Pittsburgh	KOIL	Omaha
WBZA	Springfield	WHK	Cleveland	WREN	Kansas City
WEAN	Providence	WSPD	Toledo	WLW	Cincinnati
WICC	Bridgeport	WXYZ	Detroit	WCKY	Cincinnati
WFIL	Philadelphia	WOWO	Fort Wayne	WSAI	Cincinnati
WBAL	Baltimore	WENR-WLS	Chicago	WRTD	Richmond
WMAL	Washington	KWK	St. Louis	WAPY	Albany
WSYR	Syracuse	WMT	Cedar Rapids	WJTN	Jamest'n,N.Y.
WHAM	Rochester	WTCN	Minneapolis-St. Paul	WLEU	Erie

Supplementary Facilities

WFEA	Manchester, N. H.	WFBC	Greenville	KVOD	Denver
WBRE	Wilkes-Barre	WWNC	Asheville	KLO	Ogden
WSAN	Allentown, Pa.	WIS	Columbia	KIDO	Boise
WORK	York, Pa.	WCSC	Charleston	KGIR	Butte
WCOL	Columbus, O.	WJAX	Jacksonville	KPFA	Helena
WGL-WOWO	Ft. Wayne	WFLA-WSUN	Tampa	KGHL	Billings
WOOD	Grand Rapids	WIOD	Miami	KSEI	Pocatello, Ida.
WBOW	Terre Haute	WMC	Memphis	KTFI	Twin Falls, Ida.
WGBF	Evansville	WSB	Atlanta	KGO	San Francisco
WEBC	Duluth-Sup'r'r	WBRC	Birmingham	KECA	Los Angeles
KSOO-KELO	Sioux Falls, S. D.	WJDX	Jackson	KEX	Portland, Ore.
KANS	Wichita	WSMB	New Orleans	KJR	Seattle
WTAR	Norfolk	WALA	Mobile	KGA	Spokane
WPTF	Raleigh	WROL	Knoxville	KFBK	Sacramento
WSOC	Charlotte	WAVE	Louisville	KWG	Stockton
		WSM	Nashville	KMJ	Fresno
		WTMJ	Milwaukee	KERN	Bakersfield
		WIBA	Madison		

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ALABAMA

Regional Meetings.—The fall meeting of the Northeastern Division of the Alabama State Medical Association was held September 22 in Anniston. Among the speakers were Drs. James N. Baker, Montgomery, state health officer, on "Future Plans and Needs of the State Department of Health"; Seale Harris, Birmingham, "Gastrointestinal Symptoms and Management of Pellagra"; John W. Boggess Jr., Guntersville, "Some Clinical Observations in Asthmatic Cases"; Charles N. Carraway, Birmingham, "Intravenous Sodium Pentothal and Oxygen Anesthesia"; Bishop B. Warwick, Talladega, "Nasal Headaches" and Jerre Watson, Anniston, "Some Errors in Diagnosis."——At a meeting of the Southeastern Division in Dothan August 11 the speakers were Drs. Gordon R. Smith, Ozark, on "Treatment of Chronic Ulcers"; Hugh Dent Johnson, Montgomery, "Modern Management of Acute Intestinal Obstructions"; Clarence R. Bennett, Eufaula, "Coma and Its Differential Diagnosis"; Archie E. Thomas, Montgomery, "Treatment of Syphilis in Pregnancy," and John L. McGehee, Memphis, Tenn., "Use of Living Fascial Transplants in Repair of Certain Types of Hernia."

ARIZONA

Harlow Brooks Navajo Clinical Conference.—The third Harlow Brooks Navajo Memorial Clinical Conference was held at the Sage Memorial Hospital, Ganado, August 29-31. Louis H. Evans, D.D., Pittsburgh, president, Board of National Missions, Presbyterian Church, gave the welcoming address. In addition to clinics, the following papers were presented:

Dr. Philip Lee Travers, Gallup, N. M., The Development of the Work of Sage Memorial Hospital and the Harlow Brooks Memorial Navajo Clinical Conference.
Dr. Bowman C. Crowell, Chicago, Bone Sarcoma.
Dr. Carl F. Rusche, Los Angeles, Urinary Extravasation.
Dr. John H. Patterson, Phoenix, Local Anesthesia in Major Surgery.
Dr. Grover C. Penberthy, Detroit, Management of Certain Lesions of the Esophagus.
Dr. William H. Daniel, Los Angeles, Proctology for the General Practitioner.
Dr. Fred H. Albee, New York, Reconstruction Surgery of the Skeleton.
Dr. Charles H. Arnold, Lincoln, Neb., Surgical Treatment of Nephroptosis.
Dr. Joseph Madison Greer, Phoenix, Observations on Another Method of Pinning Fractures of the Neck of the Femur.
Dr. E. Payne Palmer, Phoenix, A Plea for an Early Diagnosis and Radical Treatment of Gastric Carcinoma.
Dr. Victor S. Randolph, Phoenix, Bronchography in Diagnosis of Pulmonary Disease.

ARKANSAS

District Meeting.—The Tenth Councilor District Medical Society held a meeting in Fort Smith September 20 with the following speakers, among others: Drs. Ira F. Jones, Fort Smith, on "Differential Diagnosis Between Gastric and Duodenal Ulcer from the Standpoint of the General Practitioner"; William R. Brooksher, Fort Smith, "Present Status of Irradiation Therapy in Breast Tumors" and Herman W. Hundling, Little Rock, "Diverticulitis of the Sigmoid." Clinics were held at Sparks Memorial and St. Edward's Mercy hospitals.

New Cancer Foundation.—The Elise A. Lake Foundation has been organized within the past year to cooperate with the free cancer clinic of the University of Arkansas School of Medicine, Little Rock. The foundation is sponsored by the Arkansas Federation of Women's Clubs and is named in honor of the late Mrs. Elise A. Lake, Hot Springs, a past president of the federation, who for a year or more before her death was active in a statewide educational campaign for the early diagnosis of cancer. Its object "shall be mutual counsel and helpfulness in uniting the influence and service of citizens of the state, in promoting education for early diagnosis and treatment of cancer and to raise funds for the Elise A. Lake Foundation to increase facilities for diagnosis and treatment of cancer" at the university cancer clinic. The foundation is now seeking funds to carry out its work and county units are being organized. At a dinner during the biennial convention of the federation of women's clubs in May, pledges and cash amounting to about $1,200 were received. Mr. Lake, who was named honorary chairman, had previously given the foundation its first pledge of $1,000. Mrs. John F. Weinmann, Little Rock, is chairman. The late Dr. Harvey Thatcher, professor of pathology at the university medical school, was active in the organization of the foundation, and his successor, Dr. Albert F. De Groat, is now vice chairman. Physicians on the advisory council are Drs. Frank Vinsonhaler, dean of the medical school; Joy K. Donaldson, associate professor of surgery, and William B. Grayson, Little Rock, state health officer.

DELAWARE

State Medical Meeting.—The one hundred and forty-ninth annual meeting of the Delaware State Medical Society will be held in Dover at the New State House October 11-12, under the presidency of Dr. Clarence J. Prickett, Smyrna. Guest speakers will be:

Dr. Isidor S. Ravdin, Philadelphia, Surgical Problems of Hyperthyrcidism.
Dr. Maurice C. Pincoffs, Baltimore, Arterial Hypertension.
Dr. Edward A. Schumann, Philadelphia, The Classic Cesarean Section.
Dr. Lawson Wilkins, Baltimore, Hypothyroidism in Children.
Dr. Francis G. Harrison, Philadelphia, Blood Stream Infections in Urologic Cases.
Dr. Richard A. Kern, Philadelphia, Clinical Allergy.
Dr. David A. Cooper, Philadelphia, Indications for Surgery in the Treatment of Pulmonary Tuberculosis.
Dr. Thomas M. McMillan, Philadelphia, The Problem of Heart Disease as It Stands Today.
Drs. Kenneth E. Appel and James A. Flaherty, Philadelphia, Modern Trends in Psychiatric Therapy.
Dr. Raymond A. Vonderlehr, U. S. Public Health Service, Washington, D. C., Present Day Control of Venereal Diseases from a State and National Viewpoint.
Dr. Bernard P. Widmann, Philadelphia, The Status of X-Ray and Radium in Treatment of Cancer.

Dr. Morris Fishbein, Chicago, Editor of THE JOURNAL, will deliver a public address Wednesday evening October 12 on "The National Health Program and American Medicine."

ILLINOIS

New County Sanatorium.—A tuberculosis sanatorium for Lake County is to be built near Waukegan with a PWA grant of $193,091 and a fund of $233,000 to be raised through a bond issue and a tax levy, *Hospital Management* reports. The sanatorium will have a capacity of ninety-two beds. There will also be a nurses' home and a physicians' residence.

Chicago

Golf Tournament.—Dr. August F. Daro was the first winner of the new Chicago Medical Society Championship Trophy, which is to be awarded annually to the champion in the annual golf tournament. Dr. Daro tied with Dr. Homer K. Nicoll with a score of 78 at the tournament at the Olympia Fields Country Club August 31 and the tie was played off at the North Shore Country Club September 18, with Dr. Daro the winner. Dr. Grover E. Johnson won the VanDerslice Trophy with a gross score of 79 and Dr. Harry E. Mock the Sisson Trophy for low net with a score of 32-63—95.

New Research Building for Abbott Laboratories.—The fiftieth anniversary of the founding of Abbott Laboratories, pharmaceutical manufacturers, in North Chicago, will be celebrated October 7 with the dedication of a new laboratory building. There will be a special program in the building in the afternoon following an inspection tour in the morning. The speakers will be:

Karl T. Compton, Ph.D., president, Massachusetts Institute of Technology, Cambridge, Mass., The University and the Public Welfare.
Dr. Herbert M. Evans, Berkeley, Calif., professor of anatomy, Morris Herzstein professor of biology, and director of the Institute of Experimental Biology, University of California Medical School, The Task and Spirit of Research.
Dr. Thomas Parran, surgeon general, U. S. Public Health Service, Washington, D. C., Research and Public Health.

In the evening a program will be presented at the Palmer House with the following speakers:

Harrison E. Howe, Sc.D., Washington, D. C., editor, *Industrial and Engineering Chemistry*, The Contributions of Organized Chemistry.
George D. Beal, Ph.D., assistant director, Mellon Institute, Pittsburgh, The Scientific Development of Drug Standards.
Dr. Morris Fishbein, Chicago, Editor, THE JOURNAL, The Contributions of Medicine to the Public Welfare.

The new building is three stories high with an attic and basement, providing facilities for the chemical, bacteriologic, botanic, medical and pharmaceutic research activities of this firm. In addition to laboratories it contains a micro-analytic laboratory, a library with accommodation for 20,000 volumes, hot and cold rooms for stability studies, dark rooms on each floor for the use of optical instruments, one dark room for use as a laboratory for light sensitive reactions, and an air conditioned auditorium seating 800 persons.

INDIANA

Courses in Obstetrics.—Plans are under way to offer two week courses in obstetrics regularly throughout the year for Indiana physicians under the auspices of the department of obstetrics of Indiana University School of Medicine, Indianapolis, cooperating with the Indiana State Medical Association. It is planned to offer to four physicians at each session an intensive study in obstetrics and pediatrics. While attending the courses, the physicians may reside at the Coleman Hospital at the Indiana University Medical Center. There will be no charge for maintenance or tuition during the two week period.

City Receives Cancer Clinic.—The city of Indianapolis was formally presented August 18 with the new cancer clinic at the city hospital known as Patrick Hall. Edwin L. Patrick, Indianapolis business man, made the presentation; Mayor Walter C. Boetcher accepted the clinic, in turn presenting it to Dr. George W. Kohlstaedt, president of the city board of health. The cancer clinic is the gift of the late Mrs. Kathryn Cones Patrick, who in leaving a $100,000 benefaction fund stipulated that her husband was to select the recipient. The new department, which offers complete equipment for the treatment of cancer, will be maintained from the income of a fund of $60,000; $40,000 of the original sum was used for equipment.

LOUISIANA

Society News.—The Tri-Parish Medical Association was addressed in Tallulah August 9 by Drs. John G. Snelling, Monroe, on "Medical and Surgical Aspects of Thrombocytopenic Purpura"; Dr. Arthur A. Herold, Shreveport, "A Story of Diabetes Mellitus with Evaluation of Present Day Treatment," and James B. Vaughn, Monroe, "The Reasons for the Change in Medical Economics." —— The Bi-Parish Medical Society was addressed at the East Louisiana State Hospital, Jackson, August 3, by Drs. Isidore Cohn and Eugene B. Vickery, New Orleans, on "Vascular Clinics" and "Diagnosis and Treatment of Renal Diseases, with Some of the Newer Drugs with Results" respectively.——At a meeting of the Tangipahoa Parish Medical Society at the Hammond City Hall recently the speakers were Drs. Edgar Burns on urinary infections and Conrad G. Collins, vaginitis; both are of New Orleans.

MARYLAND

Group Instruction in Antepartum Care.—The first unit for group instruction in antepartum care was recently organized in the Southeastern Health District under Dr. John A. Skladowsky, district health officer, and Miss Rae D. Serpick, supervisor of public health nurses. Each Wednesday since the first meeting about twenty-five mothers have met to receive instruction and to witness practical demonstrations of the essential points in antepartum hygiene and infant care. Later it is hoped to establish a similar plan of health education for prospective fathers.

MASSACHUSETTS

Fellowships for Psychoanalytic Training.—The Boston Psychoanalytic Institute announces three Sigmund Freud fellowships in psychoanalytic training to begin in September 1939. The fellowships are open to graduates of class A medical schools who have had at least one year of general hospital training and two years' training in psychiatry. Applications must be filed before Feb. 1, 1939. Further information may be obtained from Dr. Moses Ralph Kaufman, chairman of the educational committee, 82 Marlborough Street, Boston.

MICHIGAN

Graduate Obstetrical Training.—Dr. Sprague H. Gardiner, senior instructor in obstetrics, University of Michigan Medical School, Ann Arbor, has been appointed in charge of a course of graduate instruction in obstetrics and gynecology. He will serve under the direction of Dr. Norman F. Miller, professor and head of the department of obstetrics and gynecology at the university. The course provides for two weeks of intensive training and observation in obstetrics, gynecology and allied subjects at University Hospital. Two practicing physicians are appointed for each period. Appointees for the quarter beginning October 1 include Drs. William G. Winter Jr., Nelson H. Clark, Harry C. Irvin, Holland; Gabriel D. Bos, Marvin B. Meengs, Muskegon Heights; William R. Lyman and George Loupee, Dowagiac; Clayton H. Palmer, Cassopolis; Sabina Kessler-Frux, Bay City, and Oscar D. Stryker, Fremont.

Pneumonia Program.—The Michigan State Department of Health will begin a program this fall to place production of pneumonia serum on the same basis as other biologic products so that state produced serum may eventually be made available to all residents of Michigan. The pneumonia program in Michigan was made possible by a grant of $50,000 from the Commonwealth Fund to cover experimentation with the production of antipneumococcus serum for three years. The last legislature matched this amount, but the governor reduced it to $30,000 because of unanticipated needs of relief. Distribution will start this fall, the use of state serum being restricted to the treatment of persons for whom serum is otherwise not available. The only other restrictions are that the determination of type be made by a registered laboratory and that physicians give the department of health a report on cases in which state serum is used. Michigan now has seventy-four typing stations, all but two of which are located below the Bay City-Muskegon line, the other two being in Houghton and Marquette in the Upper Peninsula. Thus far eight serum distributing stations have been established, two in the Upper Peninsula and six in the Lower in Houghton, Marquette, Muskegon, Grand Haven, Grand Rapids, Lansing, Saginaw and Pontiac. Typing facilities are available in thirteen other counties in Lower Michigan and distributing centers will be established in these counties as rapidly as arrangements can be made with the medical societies in these counties. Present facilities will accommodate about one third of the people of the state outside of Wayne County. A subcommittee on pneumonia of the preventive medicine committee of the state medical society agreed to cooperate with the department by giving the program a prominent place on the state medical society's program and by providing speakers for the extension courses carried on throughout the winter jointly by the state medical society and the University of Michigan.

MINNESOTA

Alumni Meeting.—The Minnesota Medical Alumni Association will hold a meeting October 14, the day of the University of Minnesota homecoming football game, at the University Hospitals, Minneapolis, under the chairmanship of Dr. Harold G. Benjamin. Clinics will be conducted in Todd Amphitheater by Drs. Ralph T. Knight in anesthesia; Horace Newhart, otolaryngology; Irvine McQuarrie, pediatrics; Owen H. Wangensteen, surgery; John L. McKelvey, obstetrics; Cecil J. Watson, internal medicine, and John C. McKinley, neurology. In the evening a dinner at the Minnekahda Club will be held in honor of Dr. Jennings C. Litzenberg, retiring head of the department of obstetrics.

MISSISSIPPI

District Meeting. — Dr. George W. Crile, Cleveland, addressed the Northeast Mississippi Thirteen-County Medical Society, Amory, September 20 on "An Analysis of the Indications and End Results of Surgical Treatment in 425 Cases of Essential Hypertension." Dr. J. Rice Williams, Houston, discussed "X-Ray Therapeutics" and Dr. William A. Evans, Aberdeen, "Preventing Pneumonia."

MISSOURI

Lectures on Obstetrics and Pediatrics.—The Missouri State Medical Association is sponsoring a series of lectures throughout the state on obstetrics and pediatrics as a continuation of a program begun in July. The speakers are Drs. Oscar F. Bradford, Columbia, and Paul F. Fletcher, St. Louis, who address lay groups the first four days of a week, on the importance of visiting a physician early in pregnancy, continuing under the physician's care until the baby is born and at least 1 year old. On the afternoon or evening of Friday of each week a meeting of physicians of the counties, sponsored by the medical societies, will be addressed by Dr. Fletcher and Dr. Bradford.

NEW HAMPSHIRE

Blood Test Required for Marriage License. — New Hampshire's law requiring a blood test for syphilis of all persons seeking licenses to marry, enacted in August 1937, became effective October 1. Before a town or city clerk issues a license, he must have in his possession a physician's statement that neither applicant is afflicted with syphilis or if afflicted is not in a stage in which the disease may become communicable. This statement must be accompanied by a record of a standard blood test. The result of the laboratory test is confidential and does not become part of the marriage record. To be acceptable the test must be made at the state laboratory

of hygiene at Concord. No charge is made for the laboratory service. Out of state applicants must conform to the requirements laid on New Hampshire residents.

NEW JERSEY

State Society Checks Need for Medical Care.—In connection with its survey of the need and supply of medical service, the Medical Society of New Jersey in July invited every person in New Jersey in need of medical care and unable to obtain it to communicate with the society's office in Trenton. The announcement was made through newspapers and radio channels. The society reports that in the first ten weeks 120 requests were received and all were turned over to the medical societies in the counties in which they originated. The requests were promptly investigated and care provided when it was needed. It was found that many requests came from persons who had already had medical care but were dissatisfied for various reasons. Requests came principally from persons who had no funds and did not know how to go about obtaining medical care. The society's report points out that 120 persons who apparently believe themselves unable to obtain medical care is a small proportion out of a state population of more than four million, that care was actually provided for some who did not know how to obtain it, and that newspapers lauded the plan as an effort to make medical care available.

NEW YORK

Cornerstone Laid for New Academy Home.—The Rochester Academy of Medicine held an official ceremony of laying the cornerstone of its new home August 22. A residence, presented to the academy recently by the daughters of the late Edmund Lyon, is being remodeled and a $60,000 auditorium is being added. Dr. Albert D. Kaiser, president of the academy in 1937, made the principal address and the present president, Dr. David B. Jewett, presided. Dr. William W. Percy has been named to a newly created position of executive director. His task will be to coordinate the functions of the academy and to supervise the moving into the new building. The former home of the academy has been sold to the University of Rochester.

New York City

Hospital News.—The New York Polyclinic Medical School and Hospital announces the opening of the urologic department in its new clinic building under the supervision of Drs. Joseph F. McCarthy, Daniel A. Sinclair, David Geiringer and Howard S. Jeck and their associates.

Unusual Prevalence of Whooping Cough.—More than 400 cases of whooping cough are being reported weekly to the New York City Department of Health, it was announced September 4. So far this year there have been 8,552 cases with seventy-two deaths. In the corresponding period of 1937 there were 2,646 cases and twenty-nine deaths, it was said.

Meetings of the Academy.—The New York Academy of Medicine announces a change in policy for its stated monthly meetings. To stimulate interest, programs for the coming year have been arranged to provide consideration of controversial issues. In certain instances, according to the *Bulletin*, discussion has been devised to invite conflicting opinions on measures now before the medical profession. The first meeting will be held October 6 and the subject will be "Evaluation of Sulfanilamide Therapy." Dr. Eli K. Marshall Jr., Baltimore, will speak on "Fundamental Problems of Chemistry and Pharmacology—Mechanism of the Action" and Dr. Reuben Ottenberg, "Clinical Aspects." The discussers will be Drs. Francis G. Blake, New Haven, Conn., on erysipelas; Emanuel Appelbaum, meningitis; Homer F. Swift, rheumatic fever; William E. Studdiford Jr., gonorrheal conditions and postpartum infection.

Attempt to Smuggle Narcotics in Ice Cream.—Three men were arrested as would-be smugglers of narcotics September 20 on evidence showing they had attempted to send 77 grains of heroin to two prisoners who were being questioned in the office of the United States marshal. The men ordered ice cream and sandwiches to be delivered from a restaurant to the two prisoners. When it was prepared the men asked to see the ice cream, and the man at the counter saw the customer put something in the package. When the men had gone the restaurant clerk telephoned the marshal's office, where investigation revealed the capsule of heroin. The three men were already under indictment for conspiracy to violate the narcotic law and were arrested in court after they had pleaded guilty to the first charge. One was sentenced September 23 to eight years in prison on the old indictment; sentence for the other two was deferred. The two men for whom the smuggled heroin was intended were also sentenced on the same old indictments to terms of three and eight years.

NORTH DAKOTA

Special Society Organized.—The North Dakota Society of Obstetrics and Gynecology was recently organized with the following officers: Drs. James F. Hanna, Fargo, president; John H. Moore, Grand Forks, vice president, and August C. Orr, Bismarck, secretary.

OHIO

Regional Annual Meeting.—The ninety-fourth annual meeting of the Northwestern Ohio Medical Association will be held in Defiance October 4 under the presidency of Dr. Edward B. Pedlow, Lima. Among the speakers will be:

Dr. Harold N. Cole, Cleveland, Precancerous Dermatoses and Malignancy of the Skin.
Dr. Robert L. Schaefer, Detroit, Clinical Indications for the Anterior Pituitary-like Hormone.
Dr. William Halsey Barker, Baltimore, Sulfanilamide.
Dr. Henry W. Meyerding, Rochester, Minn., Displacement of the Lumbosacral Spine Associated with Backache.
Dr. Emil Novak, Baltimore, Endocrine Aspects of Sterility.

The meeting will be preceded by a golf tournament Monday afternoon October 3.

OKLAHOMA

Courses in Venereal Disease.—With funds appropriated under the LaFollette-Bulwinkle bill, a series of lectures for physicians on venereal disease will begin October 3 in four counties to run for five weeks. The lectures will be given Mondays at Claremore, Rogers County; Tuesdays at Pawhuska, Osage County; Wednesdays at Bartlesville, Washington County, and Thursdays at Vinita, Craig County. Dr. David V. Hudson, Tulsa, will be the lecturer.

OREGON

Gift to University Medical School.—A gift of funds has been made to the University of Oregon Medical School, Portland, by Mrs. Julius L. Meier and her family in memory of the late Gov. Julius L. Meier. The initial gift amounts to $50,000, it is announced, and will be added to funds for construction of the new University State Tuberculosis Hospital to be built on the university grounds. The legislature appropriated $110,000 and the PWA allotted $90,000 for the hospital; the added $50,000 will make possible construction of forty beds in addition to the thirty-nine originally planned, Dr. Richard B. Dillehunt, dean of the medical school, announced. It will also make possible better outpatient facilities, it was said.

PENNSYLVANIA

Expand State Tuberculosis Facilities.—A new surgical unit at the State Sanatorium for Tuberculosis, Hamburg, was dedicated July 7 by Dr. Edith MacBride-Dexter, state secretary of health. Cornerstones were laid August 18 by Dr. MacBride-Dexter for a main infirmary, a children's preventorium and a dormitory for women employees at Pennsylvania State Tuberculosis Sanatorium, South Mountain.

District Meeting.—Dr. Martin E. Rehfuss, Philadelphia, addressed a meeting of the Second Councilor District, Medical Society of the State of Pennsylvania, Norristown, September 15, on "Gastric Neuroses." Dr. Frederick J. Bishop, Scranton, president of the state society, spoke on "The Status Quo of Medicine" and other state officers discussed current problems. Testimonials were presented to the following physicians who have been in practice fifty years: Drs. John L. Bower, Birdsboro; William T. Sharpless, West Chester; U. Grant Gifford, Kennett Square, and Nathaniel C. Peters, Northampton.

Philadelphia

Refresher Course for Nurses.—The Philadelphia General Hospital will offer a special four weeks refresher course to graduates of its school of nursing beginning October 1. One week will be spent in each of the major services (medicine, obstetrics, surgery and pediatrics), with experience in various special departments. The course will be repeated in January, April and June 1939. Graduates of the hospital who wish to take the course may communicate directly with the Director of Nursing, Miss Loretta M. Johnson, at the hospital.

UTAH

State Medical Election.—Dr. George M. Fister, Ogden, was named president-elect of the Utah State Medical Association at its annual meeting in Ogden September 1-3 and Dr. Claude L. Shields, Salt Lake City, was installed as president. Vice presidents elected were Drs. George L. Rees, Smithfield; Harry S. Scott, Salt Lake City, and Bliss L.

Finlayson, Price. The next annual meeting will be in conjunction with the Rocky Mountain Medical Conference in Salt Lake City, September 5-7, 1939.

VIRGINIA

Changes in Health Departments.—Rockbridge County has recently been separated from the Alleghany-Botetourt-Rockbridge health district to form a unit with the city of Lexington, with Dr. Robert P. Cooke continuing as health officer. Dr. James H. Gordon, Covington, has been appointed health officer of the new district of Alleghany and Botetourt counties. Dr. William Y. Garrett, Raven, has succeeded Dr. James N. Dudley, Eastville, as health officer of Northampton County. Dr. Charles H. Bondurant, Wytheville, has been made health officer of Wythe County and Dr. Eugene Bowie Shepherd, Baltimore, assistant health officer of Pittsylvania County.

WISCONSIN

Lectures on Infectious Diseases.—A series of lectures on infectious diseases will be presented by the committee on postgraduate education of the Medical Society of Milwaukee County with the following speakers: Drs. Henry C. Sweany, Chicago, on "Pulmonary Tuberculosis," October 10; John A. Kolmer, Philadelphia, "Value of Serums and Vaccine in General Medicine," October 18, and Joseph Brennemann, Chicago, "Contagious Diseases of Childhood," November 1.

WYOMING

State Medical Election.—Dr. John H. Goodnough, Rock Springs, was named president-elect of the Wyoming State Medical Society at its annual meeting in Laramie August 7-9 and Dr. John D. Shingle, Cheyenne, was installed as president. Dr. Marshall C. Keith, Casper, is secretary. The 1939 meeting will be held in conjunction with the Rocky Mountain Medical Conference in Salt Lake City, September 5-7.

GENERAL

Rocky Mountain Tuberculosis Conference.—The fourth biennial meeting of the Rocky Mountain Tuberculosis Conference will be held October 7-8 in Salt Lake City at the Hotel Utah. Twelve Rocky Mountain states make up the conference, of which Dr. Harry J. Corper, Denver, is president. Among the speakers will be:

Drs. John Zarit and Allen D. Riemer, Denver, Colo., Syphilis of the Lung.
Dr. Edward E. H. Munro, Grand Junction, Colo., Silicosis.
Dr. Leslie P. Anderson, Elma, Wash., Development of Allergy in Relation to Tuberculous Lesions in Young Adults.
Dr. Charles J. Kaufman, Denver, Vocational Therapy in the Mangement of Pulmonary Tuberculosis.
Dr. Kendall Emerson, New York, The Philosophy of the National Tuberculosis Association on Rehabilitation and After-Care.
Dr. Walter I. Werner, Albuquerque, N. M., Tuberculous Tracheitis.

At a banquet Friday evening Dr. Corper will deliver his presidential address on "Neo-Hippocratic Tuberculosis" and Dr. James J. Waring, professor of medicine, University of Colorado School of Medicine, Denver, will be the guest speaker on "Prognosis in Tuberculosis."

National Safety Congress in Chicago.—The Silver Jubilee meeting of the National Safety Congress will be held in Chicago October 10-14 at the Stevens Hotel. Addresses of medical interest include the following:

W. C. James, safety engineer, Portland Cement Association, Chicago, What About the Health of Quarry Workers?
Dr. Morris Fishbein, Chicago, Editor of THE JOURNAL, Personal Hygiene and Its Relation to Syphilis Control in the Food Industry.
Dr. Albert E. Russell, U. S. Public Health Service, Washington, D. C., Industry's Part in Combating Venereal Diseases.
Dr. Harold A. Vonachen, Peoria, Ill., What Can Be Done About Fatigue?
Dr. Harry E. Mock, Chicago, A Surgeon's Experience with Industrial Injuries.
Dr. Edward C. Holmblad, Chicago, Problems in the First Aid Treatment of Fractures.
Dr. Carey P. McCord, Detroit, Handicaps in the Diagnosis of Occupational Diseases.
Dr. Milton H. Kronenberg, Chicago, The Necessity for Uniform Absenteeism Records in the Industrial Health Program.
Dr. John J. Wittmer, New York, Has the Public Utilities Industry Any Occupational Health Hazards?

At the silver jubilee banquet Wednesday evening October 12 the speaker will be George E. Vincent, Ph.D., former president of the Rockefeller Foundation, New York.

Examinations in Obstetrics and Gynecology.—The American Board of Obstetrics and Gynecology announces that examinations for Group B candidates will be held in various cities of the United States and Canada Nov. 5, 1938, and Feb. 4, 1939. Application for the written examination for February must be filed with the secretary of the board before December 4. The general oral, clinical and pathologic examinations for all candidates (groups A and B) will be conducted by the entire board, meeting in St. Louis May 15-16, 1939, during the week of the annual session of the American Medical Association. Applications for the group A examinations must be filed with the secretary before April 1, 1939. For further information and application blanks address the secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh.

Central Association of Obstetricians and Gynecologists.—The tenth annual meeting of the Central Association of Obstetricians and Gynecologists will be held at the Hotel Radisson, Minneapolis, October 6-8, under the presidency of Dr. Robert D. Mussey, Rochester, Minn. Dr. Jennings C. Litzenberg, who recently retired as professor of obstetrics and gynecology at the University of Minnesota Medical School, Minneapolis, will be the guest of honor and will deliver an address entitled "The Making of a Conservative." Among the speakers will be:

Drs. Percy B. Russell Jr., and Michael J. Roach, Memphis, Tenn., B. Welchii Infections in Pregnancy.
Drs. Robert Jerome Prentiss and Warren W. Tucker, Iowa City, Cystography in the Diagnosis of Placenta Praevia.
Drs. Ralph A. Reis and Melvin B. Sinykin, Chicago, Myomectomy During Pregnancy.
Dr. Philip F. Schneider, Evanston, Ill., Prophylactic Endocrine Therapy in Surgical Menopause.
Dr. John Milton Singleton, Kansas City, Mo., The Effect of Alkaline Vaginal Preparations on the Huhner Test and Sterility.

A symposium on "Some Aspects of the Vascular Changes in Pregnancy Toxemias" is to be presented by the following members of the faculty of the University of Minnesota Medical School: Drs. Litzenberg, Maurice B. Visscher, Elexious T. Bell and John L. McKelvey. A banquet will be held Friday evening at which winners of the annual prize awards will present their papers. They are Drs. Fred L. Adair and John A. Haugen, Chicago, on "A Study of Suspended Human Muscle Strips in Vitro" and Drs. Ward F. Seeley, Roger S. Siddall and Walter J. Balzer, Detroit, on "Collapse Therapy for Tuberculosis in Pregnancy." At the banquet Dr. Mussey will deliver his presidential address on "Pelvic Pain" and Dr. Everett D. Plass, Iowa City, will speak on "The Birth of an Influence."

Government Services

Examinations for Army Medical Corps

The War Department announces an examination December 5-9, both dates inclusive, for qualification of candidates for appointment as first lieutenants in the U. S. Army Medical Corps to fill vacancies during the fiscal year 1939. The examination is open to all male graduates of acceptable medical schools who have completed one year's internship in an approved hospital and who will not be over 32 years of age at the time it will be possible to tender a commission. Boards of medical officers will convene throughout the United States to conduct the examination, which will consist of a physical examination, a written examination in professional subjects and a determination of the candidates' adaptability for military service. Licentiates of the National Board of Medical Examiners may be exempted from the written professional examination. Full information and application blanks will be furnished on request to the Adjutant General, War Department, Washington, D. C. Applications must be filed by November 19.

Public Health Service to Investigate Pneumonia

Field research projects in cooperation with state and local health departments have been established by the U. S. Public Health Service in seven states for an intensive investigation of the treatment and spread of pneumonia. Studies will be made in New Jersey, Pennsylvania, Illinois, St. Louis, Denver, New Orleans and a selected north central area in California. Three aspects will be covered: incidence of pneumonia by type, effectiveness of different serums in reducing pneumonia mortality and effectiveness of certain chemical substances in treatment. Funds will come from the regular scientific appropriation of the public health service, funds appropriated for public health purposes under the Social Security Act and state and municipal health budgets. Actual direction of the projects will be in the hands of the state or local health officers; the federal health service will lend technical assistance, act as consultant and in cooperation with local authorities tabulate and synthesize the results for publication. Public health service officers in charge of the studies are Drs. Joseph W. Mountin, Adolph S. Rumreich and Claude D. Head Jr.

Foreign Letters

LONDON

(From Our Regular Correspondent)

Sept. 10, 1938.

"The Doctor's View of War"

The medical profession plays an active part in war, and the question What should be its attitude toward war is discussed in a small book, "The Doctor's View of War," edited by Dr. Horace Joules and written by nine physicians with the collaboration of a score of others. In a foreword Prof. J. A. Ryle says that our profession may be claimed to be the only pacifist one in the world. Yet the physician has become a partner in modern war, for he pronounces men fit for service, inoculates them against infections, supervises their health and patches them up again for the ordeal of battle. Professor Ryle remarks that it is an arresting, if at present fantastic, thought that our profession, which is more international than any other, could, if well coordinated, of its own initiative put a stop to war or at least so hamper the most bellicose government as to give it pause. Internationalism, he thinks, will eventually pave the way to peace. The great war occurred after a period of remarkable advance in medical science and on the western front was free from the usual outbreaks of infectious diseases, although new diseases appeared and there was a large incidence of minor infections. In the East the old enemies dysentery, typhus and malaria were endemic. War neuroses do not differ essentially from those of peace but because the precipitating factors are more violent they are more striking. In the great war the neuroses were clinically in two groups, officially called neurasthenia and hysteria. Those in the former group would now be called anxiety neuroses. An example of the injustice of war was that it was the merest accident, sometimes depending on the whim of a superior officer, whether a man was labeled "shell shocked" and sent to the hospital or had to face a court martial and firing squad for cowardice.

Some persons extol war as "nature's pruning hook," but the only biologic advantage it has is hybridization, of which they do not appear to be aware. This has made possible new and more and more favorable combinations of characteristics, but there is no reason for thinking that modern warfare has any eugenic value comparable to its destructiveness. There are no signs of biologic significance attaching to the great war; both victors and vanquished have the same menace of a rapidly falling population. If there is a selective effect within a national group it is probably dysgenic. The most optimistic view is that modern war will wreck the structure of society without inflicting any permanent biologic damage.

A deplorable practice in recent wars is disregard of the Red Cross. Hospital ships were sunk in the great war, and an attack on a Canadian hospital at Doullens is well authenticated. In Abyssinia the Red Cross was systematically bombed, and in the hospital at Dessie an American nurse was wounded and patients and their attendants were killed. Disregard of the Red Cross and bombing of cities is seen in the wars in Spain and China. The authors suggest that we appear to be on the verge of another age of barbarism. The hope lies in the stubborn democratic spirit of certain countries, which refuses to be intimidated by the philosophers of war absolute.

What can the medical profession do to avert this great calamity? After advocating strengthening of the League mechanism for collective security, the authors suggest that the medical association of one of the great civilized and democratic countries should take the lead by summoning the medical societies of all other countries to a conference, which should issue a pronouncement declaring it to be the will of the profession that for the sake of humanity a system of collective security should be established.

A Nurse Is a "Workman"

Under the workmen's compensation act a person is entitled to compensation for an accident arising in or out of his employment, but this has sometimes given rise to the question What constitutes employment? Are professional footballers or film stars employed in the legal sense? A decision of considerable importance to hospitals has been given in the case of a nurse who, acting under the directions of a ward sister in a municipal hospital, was preparing a poultice which exploded in the can in which it was being heated and injured her. She applied in court for compensation, but the judge held that she was not acting under a contract of service but under a contract to perform a service as an independent expert. The case was taken to the court of appeal. An argument took place as to whether a distinction could be drawn, as in a previous case, between the skilled technical duties of a nurse and her administrative or ministerial duties (which constituted employment without any doubt). One judge thought that it could and that when she was doing her work as a nurse the hospital was not liable to pay damages for her negligence or to compensate her. But the two other judges disagreed, and so she won her case. One said that her contract of service could not be divided and that, although the hospital might choose the person whom she was called on to obey, she was always under obedience to the hospital. The other judge said that negligence cases could not be applied to the question at issue. So manifestly were nurses in the service of their hospital that for this very reason it was necessary in a negligence case to inquire whether the hospital was liable for their negligence. The nurse was the servant of the hospital for general purposes and was under a contract of service with it under the workmen's compensation acts. The case was therefore sent back to the lower court for the judge to assess the compensation payable. The hospital was given leave to appeal to the highest court, the House of Lords.

Sir David Wilkie

The Edinburgh medical school has sustained a great loss by the death, at the age of 56, of Sir David Wilkie, professor of surgery. Born in Kirriemuir, the "Thrums" of the novelist J. M. Barrie, who was an intimate friend, he was educated at the University of Edinburgh, from which he graduated in 1904. In 1909 he took the Ch.M. degree and received a gold medal for his thesis. He became a fellow of the Royal College of Surgeons of Edinburgh in 1907 and of the similar college of England in 1918 and was made an honorary fellow of the American College of Surgeons in 1926. He was not only a great surgeon and a great teacher but an active member of many scientific boards, such as the Medical Research Council and the Scientific Advisory Committee of the British Empire Cancer Campaign, and was president of the section of surgery at the Edinburgh meeting of the British Medical Association in 1927.

The conservative treatment of acute infections was perhaps the most important part of his impressive teaching. The operative zeal which naturally followed Lister's great discovery was followed today, he said, by a fundamental change, as surgeons thought more on biologic and less on mechanical lines. The delicate and complex series of local and general changes which were the reaction to local infection had as their main objects localization of the infection and mobilization of the body forces. Nothing should be done which interfered with this process. At the recent annual meeting of the British Medical Association he opened the discussion on septic hand. He held that the profession had not sufficiently recognized the value of Bier's treatment. If the infection could be localized for only a short while, time was gained for general defense. His method was to apply the thin elastic bandage very lightly to the upper arm and leave it on for not less than twenty-two of the twenty-four hours, preferably continuously, for three days. If the bandage was applied correctly there would be no duskiness of the limb, only slight swelling, and the pain would be relieved. Incision of a

boil on the supposition that it is a form of abscess he held to be wrong in theory and mischievous in practice. Complete immobilization by strapping was the best treatment, and this held also for carbuncle, though in cases of severe toxic involvement antitoxic serum should be given. Experiments on rabbits convinced him that there was no active surgical treatment for general peritonitis. It might be prevented by timely surgical intervention and complications might require surgical aid, but confidence must be placed in medical remedies, serums, fluid replacement for vomiting, heat and morphine. Empyema he treated by aspiration, saying that the appalling death rate in the American army following open drainage of streptococcic empyema was necessary to bring home this lesson.

PARIS

(From Our Regular Correspondent)

Sept. 3, 1938.

Use of Refrigerated Blood for Armies

The war clouds hanging over European countries have given an impetus to the study of whether refrigerated, or conserved, blood can be used on a large scale at or near the front. The employment of such blood during the present civil war in Spain has shown that it is an important addition to the resources of the military surgeon. At the June 29 meeting of the Académie de chirurgie of Paris, the head of a large army hospital, Dr. Maisonnet, and Professor Jeanneny of Bordeaux, who has been one of the most enthusiastic advocates in France of the use of refrigerated blood, read a paper on the organization of a service to supply such blood during war. Extensive studies have shown that blood which has been kept at a temperature of 4 C. retains all its therapeutic qualities for from ten to fifteen days. The red blood cells, although they do not decrease in number, show slight morphologic changes such as contraction, a dentated appearance and expulsion of a part of the hemoglobin, and at the end of twenty days hemolysis can be noted. The leukocytes appear to undergo destruction as the result of refrigeration. From the chemical point of view, the blood gradually loses its dextrose content, but the phosphorus and the protein content increase, probably as the result of lysis of the leukocytes. As to the physical properties of the blood, especially its density and electrical conductivity, these show changes from the twelfth day onward. The biologic properties of the blood remain practically the same, especially as to grouping. The respiratory capacity does not show any alteration until about the twentieth day. These observations show that refrigerated blood, at least during the first week, resembles so closely fresh blood as to make it safe to use the former as a substitute. The authors cited the use of refrigerated blood during the civil war in Spain. A transfusion center was organized at Barcelona in 1936, the donors being nonmobilized civilians, especially women. From each of the 4,500 donors about 400 cc. was taken every month or so. During the first year 1,220 liters of blood was thus made available to be sent to the front either by trucks or by special automobiles equipped with electrical refrigerators similar to those in domestic use. On the insurgent side twenty transfusion centers were organized. Over 9,000 persons from 16 to 50 years of age served as voluntary donors, some of them more than twelve times. Every brigade has its transfusion service, and the blood can be given at the front by using boxes constructed on the principle of a vacuum bottle so as to keep it at the same temperature as in a refrigerator. The government surgeons use a citrated blood, whereas in the insurgent armies the whole blood method as advocated by Yudin of Moscow (described in an editorial in THE JOURNAL August 20) is employed. The results, as published in recent bulletins from both armies, have been equally satisfactory.

Maisonnet and Jeanneny are of the opinion that refrigerated blood will render valuable service in future wars. Their experience in its use in peace times is limited to citrated blood. A French military surgeon, Pilod, in 1936 offered a plan for the organization of a transfusion or hematologic service for each division consisting of a chief and three aids who are specialists in the examination of donors and recipients as well as in giving transfusions. It should be the duty of such teams to obtain blood from slightly wounded or convalescent soldiers and to keep on hand a relatively large amount of blood of different groups. First aid and casualty clearing stations would thus be provided with flasks containing 250 cc. of blood from universal donors, which can be given intravenously by any surgeon. It would rarely be necessary to obtain blood from the personnel of the hospital corps. In addition to this service at or near the front, a service would be organized in every region of the country which would have as its objective the collection of a reserve supply from civilian donors, including blood from all four groups. This blood could be sent to the front by means of airplanes or automobiles equipped with apparatus to keep the blood at a low temperature. Professor Jeanneny, so that automobiles with refrigeration facilities can be dispensed with, is studying the use of a specially constructed box to contain a large number of flasks of conserved blood which can be kept at a temperature near 4 C. and can therefore be transported by ordinary army trucks. The blood can then be warmed before being used for transfusion.

Program of Therapeutic Union Meeting

This year's meeting of the Therapeutic Union will be held on October 12 at the Paris Medical School. The president is Prof. Maurice Loeper, and reports on the following subjects will be read: oxygen therapy, protein therapy of diabetes, vitamin therapy of diseases of the digestive apparatus, chlorophyll and cutaneous diseases, and continuous intravenous injection as a therapeutic method. A series of papers will be read on the part of sulfur in therapeutics. Information regarding the meeting may be obtained by writing to Dr. G. Leven, 24 rue de Téhéran, Paris 8.

French Syphilology and Dermatology Congress

This year's Syphilology and Dermatology Congress will be held in Paris October 12-14. The president is Dr. Milian, and the program includes reports on balanoposthitis by Dr. Bory, Professor Farre and Dr. Golay; on histamine in dermatosyphilology by Drs. Weissenbach and Jaussion and Dr. Kitchevatz of Yugoslavia, and on agranulocytosis in dermatovenereology by Dr. Touraine, Professor Watrin, and Professor Marin of Montreal.

BERLIN

(From Our Regular Correspondent)

Aug. 22, 1938.

Hospitals in the German Reich in 1936

A comprehensive statistical report for the year 1936 on hospitals of the German reich has just been published. The total number of hospitals was 4,792 as against 4,864 in the year 1935. Of the total number 2,106 were classed as public, 1,552 as communal and 1,134 as private. The smaller number as against the year 1935 was due to the discontinuation of most of the smaller units, namely those having twenty-five beds and less. On the other hand, the number of regularly available hospital beds in the entire country had somewhat increased; it was 620,751 as against 614,888 in 1935. Accordingly there were available an average of 92.2 regular sick beds per 10,000 of population as against ninety-two in 1935.

The number of beds available in various classes of institutions enumerated in 1936 are set forth in table 1.

The gross number of patients treated in the nation's hospitals was 3.7 per cent higher than in 1935. The distribution of patients according to sex is shown in table 2.

As a consequence of the increased number of admissions the number of sick days spent in hospital increased by about 2.8 per

cent, reaching 180,552,492. Accordingly, despite the further decline in the average per patient stay in hospital, which sank from 35.2 to 34.9 days, the utilization of beds was extraordinarily greater, reaching nearly 80 per cent of capacity.

According to season the highest average patient population fell in November; the next highest averages were in February and March. The fewest admissions took place in April.

TABLE 1.—*Beds Available in 1936*

Classification	Number	Beds
General hospitals	3,196	338,683
Hospitals for tuberculous adults	187	24,319
Hospitals for tuberculous children	31	4,841
Nursling and children's hospitals	154	14,601
Orthopedic hospitals	47	9,080
Eye hospitals	102	3,153
Hospitals for treatment of venereal diseases and dermatoses	36	2,833
Hospitals for chronic invalids and incurable patients	117	19,536
Hospitals and sanatoriums for mental diseases	260	154,032
Institutions for the feebleminded	64	23,670
Hospitals for nervous disorders	52	2,977
Hospitals for alcoholic and other addicts	18	807
Lying-in hospitals	204	9,358
Other specializing institutions	225	9,513
Hospital units in penal institutions	99	3,348

The gross number of deaths in all German hospitals is shown in table 3.

Although the mortality during the years from 1932 to 1934 remained at the same level, 4.7 per hundred patients, the rate rose to 4.8 in 1935 and to 4.9 in 1936. The influenza epidemics may be presumed to have played a part in this increase. Other possible factors are the increase in serious accidents following the revival of industry and the increasing tendency in recent years to hospitalize seriously ill patients a short time prior to death. Attention was recently called to the latter trend by the municipal medical councilor of Berlin (THE JOURNAL, April 30, 1938, p. 1501). Of 100 deaths within the German reich during 1936, 31.9 occurred in hospitals as against only 26.7 in the year 1932.

Table 4 illustrates the distribution of various types of obstetric cases.

TABLE 2.—*Distribution of Patients by Sex*

Year	Total	Male	Female
1935	4,994,000	2,352,000	2,642,000
1936	5,177,000	2,449,000	2,728,000

TABLE 3.—*Number of Deaths*

Year	Total Persons Dying in Hospital	Male	Female
1934	215,561	112,687	102,874
1935	241,883	125,874	116,009
1936	254,127	133,735	120,392

The number of completed confinements in all hospitals increased by about 6.8 per cent as against the year 1935. On the other hand, the number of artificial interruptions of pregnancy performed in hospitals declined by about 28 per cent, apparently as a result of stricter control of the necessitating circumstances.

Particularly important to the national eugenic health policy is the determination of the proportion of institutional births to the total number. In 1936 1,312,053 babies were born in Germany; the per mille proportion of babies born in hospitals was 269.9 as against 251.2 in 1935. The number of institutional births has accordingly undergone not only an absolute increase but an increase in proportion to the total number of births. The birth rates of certain localities have declined considerably as a result of increased hospitalization in confinement cases.

In the report under discussion, data on the hospitals of Austria are submitted for the first time since the country was annexed. In the year 1936, 287 hospitals were enumerated, fifteen of them institutions for the insane. There were ninety-six public hospitals with a total of 36,505 beds; 12,366 beds, namely one third of the total, were in hospitals for the insane. There were 191 nonpublic hospitals with a total of 15,682 beds; included in this group were five small hospitals for the insane with 553 beds and forty-seven sanatoriums with 2,679 beds. The total number of beds available in Austrian hospitals was accordingly 52,187 (77.8 per 10,000 of population); the bed capacity was thus smaller by some 14.4 per 10,000 than that of the German reich.

The supply of hospital beds differed widely in the various provinces of the Austrian federation. In Vienna, for example, there were 95.6 beds per 10,000 of population; for Burgenland, on the contrary, the corresponding figure was only 14.4.

The total number of persons hospitalized in Austria in 1936 was 583,171, of whom 21,080 were treated in hospitals for the insane. The total number of days in hospital was 16,051,928, of which 5,026,434 represented days spent in hospitals for the insane. The average stay in hospital was 27.6 days. The beds utilized represented 84 per cent of capacity, a somewhat larger proportion than in the German reich. During the year 23,937

TABLE 4.—*Distribution of Obstetric Cases*

Confinements	Total Number	In Lying-in Hospitals and Services	Percentage
1935	321,310	248,638	77.4
1936	349,092	264,809	75.9
Induced Abortions			
1935	4,151	1,905	45.9
1936	2,982	1,301	43.6
Miscarriages			
1935	87,182	33,422	38.3
1936	88,667	35,817	40.4

persons died in hospitals, namely 4.1 per cent of the patient population and 26.9 per cent of all persons dying in Austria in 1936.

Dosage of Ultraviolet Radiation

Dr. Wucherpfennig's fundamental discussion of the dosage of ultraviolet radiation before the medical society of Münster, Westphalia, was based in part on his own investigation. Even if the practitioner has at his disposal a dosimeter for ultraviolet rays he is still in no position to evaluate accurately the biologic reaction of predilection in the individual case. It is assumed that the dosimeter will register precisely the most important biologic reaction, namely the erythema. The erythema, however, as has been demonstrated by the author and others, is peculiarly dependent on the sex and age of the patient and the nature of the disorder. Then too, erythema varies in character according to the region of the body irradiated. Difficulties which cannot be excluded from administration of even the most optimal physical dose may, however, be abolished if the operator gages his therapeutic procedure by the erythema itself or, as Wucherpfennig calls it, the "erythematous threshold." For practical purposes one may consider this erythematous threshold of the ultraviolet current to be the weakest degree of reddening which is sharply defined against the adjacent unirradiated region within twenty-four hours after irradiation. The roentgen therapy then consists of some ten additional doses of radiation, administered at intervals of one week. Each dose must be about 30 per cent more powerful than the preceding one. This holds true for all ultraviolet current apparatus. The apparatus, for example the mercury quartz lamp and almost all carbon arc lamps with metallic salt carbons, usually emits

a short wave, erythema-producing, ultraviolet ray (an ultraviolet concentration of from 2,800 to 2,400 angstroms). Recent studies of the intermediary metabolism have demonstrated impressively the importance of the mentioned variations up to the average ultraviolet reaction. The investigations, although seemingly of only theoretical worth, have throughout a practical value as well. Cutaneous reactions to the ultraviolet rays produce, according to the degree of their intensity, metabolic processes which may be wholly disparate in character.

BELGIUM

(From Our Regular Correspondent)

Aug. 20, 1938.

The Order of Physicians Established by Law

The Chamber of Representatives has passed legislation establishing an Order of Physicians. This marks a red letter day in the history of the Belgian medical profession. Although for this body the new enactment represents the fruit of tentative negotiations which have been in progress for over a century, it may be said that the question has entered a phase of imminent realization only since 1924. In that year the Académie royale de médecine formally advocated the establishment of an official order of physicians. In recent years we have noted the successive steps in the evolution of this great reform, the social importance of which is well recognized. It seems appropriate to quote the memorable words of the minister Jaspar with regard to this problem: "When an important group such as the medical profession concerns itself with problems of deontology, morale, dignity and honor, it is a matter of interest not only to physicians. The new order of physicians, besides serving as a vital factor in the perpetuation of an organized medical profession, will serve as a strong bulwark to society as a whole." The new statute constitutes a veritable magna carta of Belgian medicine. Its more important provisions are as follows:

The Order of Physicians comprises all doctors of medicine, surgery and obstetrics resident and authorized to practice in Belgium whose names appear in the order's official register. Transitional regulations provide that all doctors of medicine, surgery and obstetrics resident in Belgium who wish to practice in this country must first have themselves enrolled on the order's official register. A provincial council of the order, having local jurisdiction over a particular practitioner, cannot refuse to enroll him unless he has been convicted of some act serious enough to warrant permanent exclusion from the practice of medicine in Belgium.

A physician barred from practice can demand and receive a personal hearing before the council of the order. He may be represented by one or several advocates. The council of the order will explain the motivation of its judgments as rendered.

There is created in each province a council of the order, having jurisdiction over all physicians resident in the province. The councils of the order are charged with upholding the standards of medical deontology, honor, propriety and dignity in their respective memberships. The councils also take cognizance, as competent authorities, of any instances of malpractice allegedly committed within the respective jurisdictions. The councils are empowered to regulate the scale and amount of professional fees in certain cases, namely (1) if serious lack of professional ethics is imputed, (2) on the joint request of two interested parties and (3) in compliance with a judicial request for expert opinion. No physician can be made liable to punishment on religious, philosophical, political, linguistic or syndical grounds or because of his affiliation with an organization concerned with practice of medicine among a particular group or class of persons. Any interference in the foregoing domains is forbidden.

Each council of the order is composed of active members and alternate members elected by the physicians whose names appear in the official list. The number of active and alternate members to be elected is fixed by the royal decree embodied in article 23. Each of the juridical arrondissements of a province shall have at least three representatives on the council. Election of members is by secret ballot. The right of voting is limited to two thirds of the seats provided for each arrondissement. The members of the council of the order, both active and alternate, are elected from among practitioners of Belgian nationality not under 35 years of age who are residents of the particular province and whose names have appeared for at least five years on the official lists of the order. The term of office is four years; members cannot be reelected to succeed themselves. Any member of a duly organized council of the order who absents himself without legitimate excuse from attendance at two consecutive meetings may be punished by admonition or by censure. The officers of a council of the order are elected from its membership; they are the president, vice president and secretary. Each council of the order is assisted in an advisory capacity by a magistrate of first instance appointed by the king. The king also appoints an alternate magistrate under the same conditions.

The superior council of the order of physicians is elected by members of the provincial councils of the order. To complete the membership of the superior council the king appoints one active and one alternate delegate from the faculties of medicine of the universities of Brussels, Ghent, Liége and Louvain. The four universities may submit to the king a list of at least three names. The superior council of the order has its seat at Brussels. It is the duty of the superior council to provide reasoned opinions on questions of general interest; among other things it collects the decisions of various councils with a view to establishment of a body of deontologic jurisprudence. The superior council is to initiate any measures necessary for the accomplishment of its objectives. If the legality of a final decision of the superior council is questioned it may be appealed to the court of cassation. If the latter tribunal finds that a decision has violated the spirit or letter of the statute the decision is set aside. The procedure of appeal to the court of cassation, with regard to both the wording and the time allowed, follows the usual conduct of civil cases. The attorney general may petition the court of cassation for review of a decision of questionable legality. Appeal to the high court is suspensive.

Marriages

WILLIAM HAPPER, London, England, to DR. GLADYS MORGAN of Guntur, Madras Presidency, India, August 15.

WALTER H. SIMMONS JR., Pine Bluff, Ark., to Miss Ruth Wackerman in Norfolk, Va., June 18.

ROBERT LATEINER, New Rochelle, N. Y., to Miss Dorothy Kasenetz of Mount Vernon, July 6.

FRANCIS N. NIMZ, Milwaukee, to Miss Marion Phillips of Stevens Point, Wis., June 28.

WALTER S. POLACHECK, Milwaukee, to Miss Shirley Witkowsky of Chicago, June 1.

OLIVER L. PUTTLER, Milwaukee, to Miss Bergliot Hefte of Staples, Minn., June 25.

JAMES H. GRESSETTE, St. Matthews, S. C., to Miss Mary Sims recently.

CLIFFORD R. SCHNEIDER, Milwaukee, to Miss Eunice Druse, June 25.

GEORGE LIBERMAN to Miss Pearl Cooper, both of Brooklyn, June 11.

DWIGHT MARTIN to Miss Evelyn Kienitz, both of St. Paul, recently.

BERNARD R. BONNOT, Canton, Ohio, to Miss Betty Mang, June 9.

Deaths

Clifford Clarence Robinson ✠ East Chicago, Ind.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1902; fellow of the American College of Surgeons; at one time member of the board of managers of the Lake County Tuberculosis Sanatorium, Crown Point; surgeon to St. Catherine's Hospital, East Chicago, St. Mary's Hospital and Mercy Hospital, Gary, and St. Margaret's Hospital, Hammond; aged 57; died, July 12, in the Augustana Hospital, Chicago, of cerebral hemorrhage and pyelitis.

Melvin M. Franklin, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1895; member of the Medical Society of the State of Pennsylvania; fellow of the American College of Surgeons; served during the World War; on the staffs of St. Joseph's Hospital, St. Mary's Hospital, Mercy Hospital and the Jewish Hospital and the Veterans Administration; aged 63; died, July 31, at Point Pleasant, N. J., of coronary occlusion.

William Henry Tefft ✠ Colonel, U. S. Army, retired, San Antonio, Texas; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1898; entered the army as an assistant surgeon in 1903; was awarded the Distinguished Service Medal for services during the World War; rose through the various grades to that of colonel; retired March 31, 1937; aged 65; died, July 1, at Fort Sam Houston, of carcinoma of the pancreas.

Edwin A. Hamilton ✠ Columbus, Ohio; Medical College of Ohio, Cincinnati, 1891; assistant professor of surgery, Ohio State University College of Medicine; fellow of the American College of Surgeons; past president of the Columbus Academy of Medicine; served during the World War; on the staffs of the White Cross Hospital and the University Hospital; aged 72; died, July 31, of arteriosclerosis and cerebral hemorrhage.

Samuel Walthall Budd ✠ Richmond, Va.; Johns Hopkins University School of Medicine, Baltimore, 1909; formerly associate professor of pathology and embryology at the Medical College of Virginia; member of the American Society of Clinical Pathologists; on the staffs of the Retreat for the Sick, and St. Luke's Hospital, Richmond, and the Petersburg (Va.) Hospital; aged 55; died, July 27, of heart disease.

Charles Emeric Kerr Vidal, Troy, Mont.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1890, and University of Bishop College Faculty of Medicine, Montreal, Que., 1890; member and past president of the Medical Association of Montana; served during the World War; at one time superintendent of the Montana State Tuberculosis Sanitarium, Galen; aged 68; died, June 20.

Rudolph Rix, Omaha; John A. Creighton Medical College, Omaha, 1899; member of the Nebraska State Medical Association; formerly professor of gynecology and clinical gynecology at his alma mater; past president of the Omaha-Douglas County Medical Society; on the staffs of the Evangelical Covenant Hospital and the Douglas County Hospital; aged 67; died, July 14, of coronary thrombosis.

Edward Ryan, Kingston, Ont., Canada; Queen's University Faculty of Medicine, Kingston, 1889; formerly professor of psychiatry and associate professor of surgery at his alma mater; at one time mayor; served during the World War; in 1927 was appointed director of hospital services for the province of Ontario; formerly superintendent of the Ontario Hospital; died, July 23.

Charles Rex Kennedy ✠ Omaha; University of Nebraska College of Medicine, Omaha, 1905; professor of clinical surgery at his alma mater; fellow of the American College of Surgeons; surgeon to the Nebraska Methodist Episcopal Hospital; division surgeon to the Union Pacific Railroad; aged 56; died, July 29, in Nevis, Minn., of pulmonary edema.

Francis J. Brennan, Oshkosh, Wis.; Marquette University School of Medicine, Milwaukee, 1931; member of the State Medical Society of Wisconsin and the Radiological Society of North America; aged 34; on the staff of the Mercy Hospital, where he died, July 7, of duodenal ulcer, hemorrhage and acute bilateral nephritis.

John A. K. Birchett Sr. ✠ Vicksburg, Miss.; Medical Department of Tulane University of Louisiana, New Orleans, 1891; past president and secretary of the Warren County Medical Society; on the staff of the Vicksburg Infirmary; aged 71; died, July 22, of coronary thrombosis and arteriosclerotic heart disease.

Robert R. Curtis, Temple, Texas; University of Louisville (Ky.) Medical Department, 1894; member of the State Medical Association of Texas; formerly city health officer; on the staff of the Scott and White Hospital; aged 67; died, July 20, in a local hospital, of malignancy and mesenteric thrombosis.

Russell Edwin Olson, Milwaukee; Marquette University School of Medicine, Milwaukee, 1916; member of the State Medical Society of Wisconsin; served during the World War; on the staffs of the Misericordia and St. Joseph's hospitals; aged 44; died, July 14, of portal cirrhosis.

Howard Orville Lienhardt ✠ North Kansas City, Mo.; St. Louis University School of Medicine, 1912; served during the World War; formerly member of the school board; aged 50; on the staff of the Research Hospital, Kansas City, where he died, July 3, of bronchogenic carcinoma.

Wyllys Royce Hodges, Cumberland, Md.; Southern Homeopathic Medical College, Baltimore, 1900; member of the Medical and Chirurgical Faculty of Maryland; on the staff of the Memorial Hospital; aged 64; died, July 14, of coronary sclerosis and diabetes mellitus.

Stuckey Fleetwood McIntosh ✠ Tucson, Ariz.; Tulane University of Louisiana School of Medicine, New Orleans, 1921; at one time secretary of the Chattanooga and Hamilton County (Tenn.) Medical Society; aged 44; died, July 24, at Van Horn, Texas, of heart disease.

Thomas Theodore Sawyer © Kansas City, Mo.; University Medical College of Kansas City, 1907; veteran of the Spanish-American and World wars; aged 59; died, July 25, in the Veterans Administration, Excelsior Springs, of chronic nephritis and hypertension.

Christopher Tuttle Croddy, Portland, Ore.; Rush Medical College, Chicago, 1897; member of the Oregon State Medical Society; aged 75; died, June 26, of angina pectoris, arteriosclerosis and hemiplegia.

Henry Ferrell Carman, Butte, Mont.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; aged 63; died, July 24, in Wise River, of cerebral hemorrhage.

William Harry Hawley ✠ College Corner, Ohio; Miami Medical College, Cincinnati, 1885; member of the Indiana State Medical Association; formerly member of the school board; aged 80; died, July 6.

Oscar Clyde Page, Brodnax, Va.; University College of Medicine, Richmond, 1911; member of the Medical Society of Virginia; served during the World War; aged 53; died, July 1, of heart disease.

James Everett Pierpoint, Skidmore, Mo.; Ensworth Medical College, St. Joseph, 1899; member of the Missouri State Medical Association; aged 69; died, July 14, of coronary occlusion.

Leonard S. Krauss, Middletown, Ohio; Ohio Medical University, Columbus, 1895; aged 86; died, July 16, of arteriosclerosis, Parkinson's disease and heart disease.

Dwight Stanley Whittemore, Brockton, Mass.; Boston University School of Medicine, 1887; aged 74; died, June 25, of cerebral thrombosis and arteriosclerosis.

Peter L. Benthack, Chadron, Neb.; Kansas City (Mo.) Homeopathic Medical College, 1899; aged 70; died, June 12, of epithelioma of the lower lip.

Elizabeth Pruin Hofma, Grand Haven, Mich.; Woman's Medical College, Chicago, 1891; aged 78; died, July 2, of myocarditis and arteriosclerosis.

Samuel Houston McMahon, De Ridder, La.; Kentucky School of Medicine, Louisville, 1898; aged 74; died, July 3, of encephalitis.

Daniel Keyworth Cowley, Granby, Que., Canada; McGill University Faculty of Medicine, Montreal, 1880; aged 81; died, July 10.

John R. Holsclaw, Shepherdsville, Ky.; Louisville (Ky.) Medical College, 1875; aged 87; died, June 30, of chronic nephritis.

George L. Hines, Williamsburg, Ohio; Medical College of Ohio, Cincinnati, 1882; aged 81; died, July 15, of senile dementia.

George G. Kreeger, Richmond, Kan.; Kansas City (Mo.) Medical College, 1895; aged 65; died, July 11, of coronary sclerosis.

Thomas G. Howe, Atlanta, Texas; Memphis (Tenn.) Hospital Medical College, 1893; aged 83; died in July of senility.

Jacob Marcus, Boston; Tufts College Medical School, Boston, 1912, aged 53; died, June 22, of hypertension.

Correspondence

CALCIUM METABOLISM AND TEETH

To the Editor:—While there are some problems pertaining to dental caries which remain unsolved, there are innumerable well established facts relating to it which are widely known and generally accepted. Dr. Schour in his article on calcium metabolism and the teeth in THE JOURNAL (March 19, p. 870), logically and dispassionately stated these facts and fairly summarized the present status of dental caries. While it is not meant that his studies are complete or final, the chemicoparasitic theory to which he subscribes will not be modified and the data on which he bases his conclusions will not be disproved. It was, therefore, regrettable and confusing that an article of such outstanding merit should have been questioned by Dr. McCall (THE JOURNAL, July 23, p. 338), particularly since the criticisms were based on so little and as yet controversial evidence.

Since the days of Miller it has been almost universally accepted among scientists that decay begins externally, that the enamel is entirely passive in the process, and that the disease is caused by acids liberated by the bacterial fermentation of carbohydrates.

Periodically during the last decade, certain individuals have made many attempts, unfortunately not based on adequate scientific evidence, to revive the discarded humoral and vital theories of decay. These investigators have postulated that the enamel, through its organic matrix and lamellae, remains under metabolic and physiologic influences throughout life and therefore is not only subject to variations in its resistance to dental caries but exhibits the ability to defend and repair itself actively. The fact that devitalized and normal teeth, as far as the enamel at least is concerned, react pathologically in an identical manner and likewise and to the same extent exhibit susceptibility or immunity to dental caries, together with the fact that there is a reciprocal relationship between tooth density, permeability and caries, should be sufficient evidence to disprove the claims of those who contend that metabolism occurs in formed enamel and that on the efficiency of this process depends the incidence and progress of decay.

More recently the vital humoralists have postulated that alterations of systemic metabolism, secondary to the ingestion of modern food, cause a change in the chemical nature of the saliva, which by altering the local environment permits enamel decalcification and the development of caries. The main evidence on which Dr. McCall takes exception to the article by Schour is predicated on this as yet wholly unproved assumption: that there is a chemical difference between the salivas of caries immune and caries susceptible individuals. To date there has been no satisfactory evidence submitted that there is any difference in chemical composition of the clean saliva of the two groups. On the contrary, the evidence overwhelmingly favors the view that the saliva as it enters the mouth is chemically if not immunologically identical in the two groups.

I disagree with Dr. McCall's contention that pregnancy may influence the development of caries and that hypoplastic enamel is more susceptible to caries than normal enamel. From a review of Dr. McCall's work I have been unable to find any evidence which would justify the conclusion that "evidence is accumulating to show that at any time of life the general metabolism affects the teeth and largely determines whether or not they will decay."

In view of the already widespread acceptance of Schour's views it is somewhat anachronistic and unnecessarily alarming to contend that Schour's "conclusions might, if accepted, have possible unfortunate effects on medical practice." To date no satisfactory evidence has been submitted which would tend to favor the belief that metabolism occurs in formed enamel; therefore, in view of the really large amount of evidence to the contrary the burden of proof that it does occur must continue, of course, to rest with the exponents of the vital theories.

While it is remotely possible that the theory of chemicoparasitism may eventually prove to be inadequate to explain certain facts pertaining to dental caries, it is apparent that the contentions and evidence presented by McCall do not seriously challenge, much less demand the modification of, Miller's theory of decay.

JULIAN AMBROSE, D.D.S., New York.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

DEATH RATE AND INCOME

To the Editor:—Have you any statistics relative to the comparative death rate in the lower income group (up to $2,000 or $2,500) as it is at present and as it was twenty years ago? The statement was made recently that the death rate had declined in the upper income group on account of the better available medical facilities but that the death rate in the lower group was as high as ever.

ROBERT C. JAMIESON, M.D., Detroit.

ANSWER.—No studies comparing the death rates in the lower income classes twenty years ago with the death rates today have been found. Prior to 1930 there were no studies of mortality data according to occupation, and no statistics have been compiled on mortality rates by income classes, except for a few special studies of individual causes of death.

Mortality statistics from the Bureau of the Census show that the death rate has decreased from 15.0 per thousand in 1910 to 10.9 per thousand in 1935, or a decrease of 27.3 per cent. If the upper limit of the low income group is taken as $2,500, nearly 20,000,000 families, or 71 per cent of all families in the United States, would belong to this group (America's Capacity to Consume, Brookings Institution). Consequently the decline in the death rate during the twenty-five year period from 1910 to 1935 could not be accounted for by a decrease in mortality rate for the persons in the income group above $2,500 alone.

Likewise the Metropolitan Life Insurance Company, in a study of the mortality rate among its industrial policyholders, showed a decline of 35.8 per cent in the mortality rate during the period from 1911 to 1938 (Statistical Bulletin, Metropolitan Life Insurance Company, January 1938). The industrial policyholders of the Metropolitan were largely persons in the lower income brackets of the urban population.

From the foregoing it appears rather certain that the death rate in the lower income group has been steadily decreasing during the past twenty years.

A special study of mortality statistics according to occupation was made for ten states which in a certain way indicates the mortality rate according to the economic status of the majority in the occupational group (Death Rates by Occupation, by J. S. Whitney, based on United States Census Bureau data for 1930). For example, the mortality rate for professional men in 1930 was 7.0 per thousand, while for unskilled workers it was 13.1 per thousand.

No similar study has been made since to show whether the mortality in the occupational groups with a relatively high average economic status is declining faster than the mortality rate for occupational groups with a lower economic status. Furthermore, mortality studies according to occupational groups do not accurately show the mortality according to economic status, because the occupational hazards have a greater effect on the mortality rate than the differences in the standards of living; that is to say, a group of unskilled workers with an average income of $100 a month would be more likely to have a higher death rate than a group of professional workers with an average income of $100 a month, chiefly because of the hazards of the occupations followed by unskilled workers.

The statement that the death rate in the upper income group is lower on account of the better available medical facilities is inaccurate because many other factors are involved. As an example, *Public Health Reports* for Sept. 2, 1934, shows the results of an experiment in Liverpool, England, where the death rate from all causes for a certain slum area was reduced from 37.0 per thousand to 26.6 per thousand after the area was rebuilt with better homes and improved sanitation; with few exceptions the same population remained in the area. Likewise, agricultural workers have the lowest mortality rate of any occupational group, which indicates that occupational conditions and the standard of living are important factors in reducing mortality.

The United States Public Health Service has made a great many sample studies of morbidity and mortality in relation to economic status. In general, these studies indicate that higher illness and mortality rates among the poor are caused primarily by factors such as crowded housing conditions, lack of adequate food and clothing, and occupational hazards. The availability of medical care is also a factor.

ASCENDING PARALYSIS AND POSSIBLE SPINAL CORD COMPRESSION

To the Editor:—A man aged 48, whose present complaint is increasing paralysis of the spastic type for the last six months, has entirely lost the action of his legs. He can move both arms slightly and when he does so there is a decided tremor. Knee, ankle, biceps, triceps are all hyperactive and equal. Ankle clonus is bilateral; there is a suggestive right Babinski; the Hoffmann thumb sign is present in both hands; the abdominals are present, the cremasteric is decreased; vibration sense is normal; likewise pain, temperature and tactile sense are normal. There is no slurring of speech; the eyegrounds are normal; there is no bitemporal pallor or nystagmus; the facial expressions are normal; there is no cranial nerve involvement, headache, double vision or difficulty in swallowing. X-ray examination of the skull shows questionable early calcification of the pituitary; x-ray examination of the cervical spine shows a normal condition. The blood count, red and white, is within normal limits; the blood and spinal Wassermann reactions are negative. The spinal fluid cell count shows 2 cells; sugar (spinal fluid) 75; protein, 57. The patient is clear mentally. There is no history of injury. Occasionally there is a rise in temperature of 1 degree. The urine is essentially normal. The paralysis began with the lower extremities and is progressing upward. A neurologist is as puzzled as I am. M.D., N. Y.

ANSWER.—Increasing spastic paralysis in a man of 48, beginning in the legs and ultimately involving the arms, is suggestive of compression of the spinal cord. The facts, as given, indicate that this possibility has not been entirely ruled out. The level of the lesion is at least as high as the fifth cervical segment and the practical question arises as to whether or not evidence is present of disease of the first four cervical vertebrae. Although the roentgenograms of the cervical spine are said to show a normal condition, particular care should be directed toward a complete examination of these four vertebrae—not by any means an easy task. Tuberculous osteitis, secondary carcinoma or other neoplasms such as sarcoma, myeloma or lymphoblastoma are easily overlooked unless the roentgenograms are exceptionally good. There is evidence, moreover, of a partial block in the spinal fluid in that the total protein is 57 mg., somewhat higher than the normal limit. Unfortunately the record does not state anything with regard to the hydrodynamics of the cerebrospinal fluid, particularly the Queckenstedt test. In high spinal cord tumors this test is not of as much value as in those lower down. Nevertheless, evidence along these lines should be sought for. Of particular value in an obscure case would be a combined cistern and lumbar puncture, with a record of both responses to jugular compression and also a comparison of the amount of protein from both loci. If any signs of block should be found, an attempt should be made to visualize the exact level of the lesion, and possibly its nature, by the injection of iodized oil into the cistern, allowing it to run down in the spinal subarachnoid space. By such an examination, tumor or adhesive arachnoiditis might be disclosed. Pachymeningitis, moreover, in this region is certainly to be considered. It does not necessarily need to be on a syphilitic basis. Should evidence for a block in the cerebrospinal fluid be obtained by examinations, laminectomy with exposure of the area would be the treatment of choice.

Without sensory changes or disturbance of the sphincters, intramedullary cord tumor is unlikely, nor would one expect to find an intrinsic degenerative disease like syringomyelia. The lack of any involvement of the cranial nerves, plus the presence of the abdominal reflexes, along with the patient's age, make a diagnosis of multiple sclerosis unlikely.

It is therefore clear that, before a definite diagnosis can be made, the patient needs additional examinations. Such examinations as the combined puncture, the injection of iodized oil and the reading of the results by the radiologist require a good deal of skill and should not be undertaken unless a thorough understanding of the value of these examinations is available. In view of the patient's progressive paralysis, such examinations are entirely justified and operation should not be overlooked as an important means of treatment should the examinations disclose a definite compression of the spinal cord.

EHLERS-DANLOS SYNDROME

To the Editor:—Please send information concerning the Ehlers-Danlos syndrome: symptoms and treatment, if any.

ERNEST B. HANAN, M.D., Bolivar, Mo.

ANSWER.—The Ehlers-Danlos syndrome is congenital and of rare occurrence. Its subjects are not unusually objects of curiosity and are therefore exploited in cheap museums and sideshows.

There are essentially three parts to the syndrome. The skin is abnormally elastic, so that it may be pulled out to excessive distances. The favorite sites to elicit this increased elasticity are at the elbows and knees. The skin may snap back into place like a rubber band after it is pulled. Other times there is a more gradual resumption of the original outline of the skin. Noteworthy histologic changes of the skin seen in the hyperelastic regions are tortuosity of the blood vessels and undulations and increase in the elastic elements. The second cardinal feature of this syndrome is the overextensibility of the joints, especially at the base of the thumb. Finally the skin is easily injured to form thin atrophic scars. These occur most frequently about joints, especially at the elbows and knees. The type of scarring is characteristic and is the most commonly encountered sign of the triad. It is more frequent that individual signs occur alone or in combination with one other. More rarely the full syndrome of three signs appears.

Several congenital anomalies have been associated and confused with the Ehlers-Danlos syndrome. Dermatolysis, in which there are loose aprons of skin, is not to be identified with this syndrome. Related to it but not identical is the dystrophic variety of epidermolysis bullosa. The connection of Recklinghausen's disease and the Ehlers-Danlos syndrome has been discussed in the literature.

There is no suggested therapy. It is a permanent developmental anomaly.

TETANUS ANTITOXIN OR CORONARY THROMBOSIS AS CAUSE OF DEATH

To the Editor:—A patient cut one finger of one hand on a nail, Feb. 14, 1938. On the same day he was given first aid treatment and 1,500 units of tetanus antitoxin, first having been tested intradermally. Approximately one week later he had an attack of syncope, associated with precordial pain, weakness, dyspnea and loss of consciousness. At this time the family noticed that he had a generalized erythematous rash and he was taken to a hospital where he was told that he had a serum reaction. The man continued to work and approximately one week later had a second attack, when he complained of pain in his chest followed by a rapid loss of consciousness. He died in a few minutes. The only abnormalities at the autopsy were a moderate coronary sclerosis and a recent myocardial infarct, which was along the course of one of the branches of the left coronary artery. On microscopic examination it was found that the infarct had occurred from ten to fourteen days before death. The pathologist reported that the man died of coronary spasm, which was sufficient to cause death because of the already damaged infarcted left ventricle, that there was a definite connection between the tetanus antitoxin and the cardiac condition and symptoms and that he believed the tetanus antitoxin was definitely a contributory factor in the death of this man. I have talked with cardiologists who do not believe that the tetanus antitoxin was a contributing factor. Please give your opinion, with reference to the literature if there is any. M.D., Texas.

ANSWER.—A man, age unstated, had an attack of syncope, precordial pain and other symptoms, which was followed by a second and similar but fatal attack about one week later. Coronary sclerosis and myocardial infarction were demonstrated and evidently it concerned a fairly typical case of fatal coronary disease. The question is raised whether an injection of tetanus antitoxin had exercised a determining effect on the course of events. The statement mentions that an erythematous rash was present when the first heart attack came on about one week after the antitoxin was given. In view of the great variety of conditions under which such heart attacks set in it is purely speculative whether the alleged serum reaction had any part in the first attack in this case. That the serum reaction had any direct part in the second and fatal attack seems quite unlikely,

b cause it occurred a week or so after the reaction. There is no other evidence available except the apparent coincidence of the serum reaction and the first attack to support the statement tl.at "the tetanus antitoxin was definitely a contributing factor in the death" of the patient.

AREA FOR INJECTION OF PERTUSSIS VACCINE

To the Editor:—Why is the Sauer pertussis vaccine given in the arm alone? Is there some reason for injecting the vaccine in different areas of the arm or would any subcutaneous injection be all right?

CLARENCE M. O'HORA, M.D., Beaver Dam., Wis.

ANSWER.—In 1925 Madsen reported on the injection of Haemophilus pertussis vaccine containing 10,000,000,000 bacilli per cubic centimeter, a total dose of 2.2 cc. (0.5, 0.7 and 1 cc. at three day intervals). This dose usually failed as an immunizing agent, but Danish clinicians and health officers observed a milder course and fewer deaths in patients who had had the vaccine. They believed that their best results occurred in those who had a transient local reaction at the time of injection. In his vaccination against whooping cough, Sauer since 1928 has used for children under 2 years of age a total dose of 8 cc. (2, 3 and 3 cc. at weekly intervals), a total of 80,000,000,000 bacilli. He believes that a better immunity response occurs when the injections are given just under the skin. The freshly isolated cultures are grown on human blood mediums to exclude anaphylaxis and sensitization due to alien proteins.

The upper parts of the arms are the logical site for the superficial injection of such quantities of concentrated vaccine. The arms were probably chosen because the desired local reaction (immediate blanching, subsequent erythema) would cause the least inconvenience there. It is less likely to be scratched than if given on the trunk. The buttocks would entail unnecessary hazards, because of the danger of abscess from fecal contamination or excoriated skin from ammoniacal diapers.

Infection of the upper arms will not occur if the syringe and needle are sterilized by heat (oven at 250 F. for one hour, or boiling), vial cap and site thoroughly cleansed with ethyl (not "rubbing") alcohol. Wet dressings should not be applied for local redness.

PERSISTENT LEUKOPENIA

To the Editor:—Have there ever been reported in the literature such conditions as anomalies of the hemopoietic system in which the normal white cell count is extremely low? A man aged 23 on repeated examinations is found to have a white cell count of 1,500, the lowest count being 1,100 and the highest 2 000. The only significance of the differential counts is the finding of an increased number of band forms, varying from 11 to 34. The other components of the blood have been normal. The patient feels well and repeated physical examinations in the last two months have revealed nothing of significance to lead one to suspect leukemia or a true agranulocytosis. The patient was admitted to the hospital because of the low count found on a routine check-up.

M.D., Rhode Island.

ANSWER.—There occur occasionally physiologic leukopenic states lasting for years in persons in whom no primary bone marrow or secondary causative tissue or organ disorder can be found (Doan, C. A.: The Neutropenic State, THE JOURNAL, July 16, 1932, p. 194). In such cases intercurrent infections are accompanied by adequate granulocytic leukocytoses; the duration and severity of such illnesses is no greater than in those cases in which an average interim total white cell count of between 5,000 and 10,000 is shown, and bone marrow studies reflect no disturbance in the normal myeloid-erythroid ratio or in the physiologic maturation pattern of the myelocytes. Such cases reported in the medical literature, however, usually have shown a total white count maintained between 2,000 and 3,500 with normal differential white cell relationships, both qualitatively and quantitatively.

When the total white count remains persistently below 2,000 and on repeated observations may even occasionally fall below 1,000, without other readily detected signs or symptoms, as in the case cited, one must seriously consider an early Banti's syndrome. The first evidence of this disease entity may be a profound asymptomatic leukopenia. Sooner or later the spleen will become palpable and one or more of the usual liver function tests, including the bromsulphalein dye, the galactose tolerance and the hippuric acid excretion tests, will reflect hepatic damage. The bone marrow shows no inhibition or diminution of normal hemopoiesis and unless and until gastrointestinal hemorrhage occurs, occult or gross, there will be no anemia and no significant platelet changes. The leukopenia would appear to depend on a specific splenic sequestration of leukocytes because following successful splenectomy in such cases the total white count again becomes normal. There are no pathognomonic tests or physical signs in the establishment of Banti's syndrome early. The diagnosis must be made by eliminating all other possible mechanisms for the leukopenia, and the alert physician may occasionally advise prompt splenectomy in order to avert a massive esophageal hemorrhage, which so often is the first sign of the far advanced disease. Successful splenectomy in this condition depends on early diagnosis before perisplenic adhesions and venous dilatations make removal of the spleen impossible.

Leukopenia rarely, if ever, is the initial blood finding in incipient hypoplastic or aplastic anemia. When present, it is distinctly a granulopenic leukopenia and practically always is preceded or accompanied by a more or less marked thrombocytopenia or/and anemia.

True agranulocytosis also is reflected by a granulopenic white count, with absolute marrow myelopenia and immaturity, and usually is followed promptly by characteristic clinical symptoms.

Aleukemic leukemia likewise is seldom asymptomatic or without physical signs, and the quality and relative disproportionate increase of the leukemic cells should be diagnostic.

DIAGNOSIS IN SPASTIC ATAXIA

To the Editor:—A man aged 65 had pneumonia six years ago. During his convalescence he noticed stiffness, numbness and prickling sensations of his legs and feet without pain. He has had difficulty since in walking in the dark, stumbling easily, and the leg symptoms have persisted. He now has pain in the legs and his hands feel as if they were asleep. He complains of tightness around the lower part of the abdomen, beltlike in character. He weighs 172 pounds (78 Kg.) and has a blood pressure of 174/70 and a regular pulse of 100. The Romberg sign is present. He has loss of vibratory sense from the waist down. The knee jerks are slightly exaggerated; the Babinski reflex is present; abdominal reflexes are lost. There is no nystagmus. The blood count reveals 4,180,000 erythrocytes, 7,800 leukocytes, a normal differential and hemoglobin of 13 Gm. The blood and spinal fluid Wassermann, Kline and Kahn reactions are negative. There is a slight increase of globulin in the spinal fluid. The colloidal gold curve is 1112321000. There are no other symptoms or positive physical signs. Do you agree that the most probable diagnosis is subacute combined sclerosis of the spinal cord? With this blood picture, without benefit of gastric analysis, can I say that he has no primary anemia? With no history of syphilis or of observations other than those given, can I say that he does not have syphilis? What may I offer him in the way of prognosis and therapy? How should the colloidal gold curve be interpreted?

REID P. JOYCE, M.D., Ashland, Ohio.

ANSWER.—The patient has the signs and symptoms of spastic ataxia due to involvement of the posterior and lateral columns of the spinal cord (thoracic cord?). The most probable causes of this condition may be (1) pernicious anemia resulting in subacute combined cord degeneration; (2) cerebrospinal sclerosis (arteriosclerotic); (3) pneumonia; (4) cord tumor; (5) avitaminosis. To make a diagnosis of subacute combined sclerosis of the spinal cord one should find achylia gastrica (no free acid in the stomach contents). If achylia gastrica is not found, the most likely diagnosis is a pneumonic myelitis. One should do a careful manometric study of the spinal fluid to rule out a block due to a tumor. The second question cannot be answered. In 30 per cent of cases of subacute combined cord degeneration the blood picture is normal. In six years, however, there should have been a change in the blood picture if one is dealing with a pernicious anemia, unless the patient is being treated with large doses of liver. From the evidence submitted one can be fairly confident that the patient does not have syphilis. The prognosis is doubtful. The patient should be placed at absolute bed rest for a period of six to eight weeks and large doses of liver with vitamins A, B_2 and G given three times weekly by intramuscular injection. Reeducation exercises are suggested for the sensory ataxia. The colloidal gold curve is not significant of any condition. It should be considered as an atypical normal.

TREATMENT OF CONGENITAL CLUBFOOT

To the Editor:—What is the best therapy for congenital clubfoot (rigid contracted arch)? What percentage of cures are effected when the usual surgical procedures are employed?

ROBERT MONFORT, M.D., Onaway, Mich.

ANSWER.—Treatment for congenital clubfoot depends on the type of deformity, which may be varus, valgus, calcaneus, equinus or a combination of two or more of these, and also on the age of the child and the methods of treatment which have been used previously. Since the patient concerned is said to have a rigidly contracted arch, it may be safely assumed that it is not a newborn infant. Approximately 75 per cent of clubfoot deformities are of the talipes equinovarus type. When early correction has not been successful or the condition has been neglected until the deformity has become rigidly fixed with a

contracted arch, an operation is indicated. This may include section of the flexor hallucis longus tendon, posterior capsulotomy of the ankle, lengthening of the achilles tendon, or section of the adductor brevis tendon and of the plantar fascia near its insertion into the os calcis. These are the structures, either static or dynamic, which are responsible for maintenance or recurrence of the deformity. After these operative procedures the foot should be manipulated while the patient is still under the anesthetic and a cast applied to maintain a position of overcorrection. In some instances the number of operative procedures may be less than those mentioned and in other cases more. For the patient 6 years or younger, this course of treatment may be found adequate in a reasonably high percentage of cases. For patients more than 6 years of age, one has to consider the advisability of arthrodesis of some of the proximal tarsal joints. This may be indicated when there is severe deformity of the bones of the foot because of long continued malposition.

The surgeon should constantly keep in mind the fact that, while it may not be difficult to manipulate and correct the position of a clubfoot, the factors of muscle imbalance and ligament contractures must be treated in order to prevent prompt recurrence with even more serious deformity after the restraint of the cast has been removed.

Some authors have stated that 60 per cent of these cases will recur when only manipulation and cast are used in the treatment.

References:

Compere, E. L.: Congenital Talipes Equinovarus, *S. Clin. North America* **15**: 767 (June) 1935.

McCauley, John C., and Krida, Arthur: The Early Treatment of Equinus in Congenital Clubfoot, *Am. J. Surg.* **22**: 491 (Dec.) 1933.

ESTIMATION OF SPINAL FLUID PROTEIN

To the Editor:—What is the best technic for estimating the total protein in the spinal fluid? ROBERT M. HARBIN JR., M.D., Rome, Ga.

ANSWER.—The amount of protein present in normal cerebrospinal fluid is so small (under 0.1 per cent) that its accurate estimation is a matter of some difficulty. Several different procedures may be followed: 1. The total nitrogen, and nonprotein nitrogen after Folin-Wu tungstic acid precipitation, may be determined in the spinal fluid by the micro Kjeldahl method, the difference between the two determinations taken as representing the protein nitrogen and multiplied by the factor 6.25. 2. The protein may be precipitated by tungstic acid and the amount of this precipitate estimated by either (*a*) the micro Kjeldahl nitrogen estimation or (*b*) the use of Folin's tyrosine reagent (Ling, S. M.: *J. Biol. Chem.* **69**:397 [Aug.] 1926) and the amount of protein calculated by employing suitable factors [(*a*) 6.25 and (*b*) 19.1]. 3. Or more simply by precipitating the protein with some reagent such as sulfosalicylic acid and determining the amount of this precipitate nephelometrically or turbidimetrically. The last procedure was employed by Denis and Ayer (*Arch. Int. Med.* **26**:436 [Oct.] 1920) with satisfactory results and has since been used by many workers. Marjorie R. Mattice (Chemical Procedures for Clinical Laboratories, Philadelphia, Lea & Febiger, 1936, p. 387) states that she has found this method to check with the Kjeldahl procedure. The Dennis-Ayer method would appear to be the simplest satisfactory method of estimating spinal fluid protein.

SECOND COURSE OF MALARIA FOR DEMENTIA PARALYTICA

To the Editor:—The members of the staff of the hospital with which I am connected have been having some arguments of late as to the efficacy of repeating malarial therapy in dementia paralytica. Some claim that it is useless to give it more than once and others that it should be repeated. What is your opinion? M.D., Indiana.

ANSWER.—The reports which appeared in the literature for several years after Wagner von Jauregg suggested the use of malaria indicated that a second course of malaria would occasionally produce satisfactory clinical results when the first course had been unsuccessful. However, subsequent experience has not substantiated this observation and it is now generally accepted that the second malarial course will not be more successful than the first.

It is usually impossible to produce a second febrile course from reinoculation with malaria that will produce more than one or two attacks of fever, because these patients tend to arrest the malaria spontaneously. Although the blood may show Plasmodium vivax following inoculation the second time, the chills and fever do not develop. If a patient does not derive clinical or serologic benefit from a course of malaria, it is of more advantage to use one of the fever producing machines for the second fever course rather than to attempt to use the malaria a second time. Irrespective of the type of fever therapy employed, the use of arsphenamine and a bismuth compound or tryparsamide and a bismuth compound is indicated after the fever course.

CAR SICKNESS: PAROXYSMAL LABYRINTHINE DISEASE OR EPILEPSY

To the Editor:—A boy aged 12 is subject to car sickness, depending on the anxiety with which he travels to a certain destination by automobile or trolley car. He becomes pale and nauseated and is slightly uncomfortable even after riding merely a half hour. He is not so likely to become car sick while riding in an omnibus. Physical and otologic examinations reveal nothing to account for this. His eyes have recently been refracted and he is wearing proper glasses. Casual riding on a bicycle has not given him any trouble. Is there any danger from a fall if bicycle riding causes a feeling similar to car sickness? I myself have not known of such an instance, yet a neurologist has warned the boy against bicycle riding. On the other hand, is it likely that bicycling would accustom a boy to traveling so that car sickness would be mitigated when he rides in an automobile or trolley car? M.D., Pennsylvania.

ANSWER.—The diagnosis appears to be paroxysmal labyrinthine disease. In this condition the only objective finding is usually an irritable labyrinth. If this is the case there is no danger from a fall while riding a bicycle. One must be sure that one is not dealing with epilepsy. That is why the neurologist in all probability advised against riding a bicycle. It is suggested that this boy be placed on a salt free diet and given from 1.3 to 1.6 Gm. (20 to 25 grains) of ammonium chloride in a capsule three or four times daily for a period of ten days or two weeks. This condition is analogous to sea sickness, air sickness and elevator sickness.

OAK BALM SUPPOSITORIES

To the Editor:—What is the present status of the Oak Balm (Hager) Company, South Bend, Ind.?

ROBERT MONTFORT, M.D., Onaway, Mich.

ANSWER.—No analysis has been made of "Oak Balm" by the American Medical Association. Some years ago the state chemists of North Dakota analyzed Oak Balm and reported that these suppositories were composed chiefly of boric acid and alum, in a cacao base. The chemists added that "tannin was not detected, therefore no oak constituent was present." As there is nothing to prevent "patent medicine" exploiters from changing the composition of their products overnight, we are unable to state whether the ingredients given above represent the present composition of this nostrum.

LEFT HANDEDNESS IN CHILD

To the Editor:—What is the present status of treatment of left-handedness in a child? A boy aged 3 has been using his left hand in picking up and holding objects and now uses this hand to eat with almost exclusively. His use of the right hand seems awkward. Should any attempt be made to correct this? If so, what is the best procedure? M.D., Pennsylvania.

ANSWER.—It is considered unwise to attempt to coerce a distinctly left-handed child to use his right hand as the dominant one. There is some justification in making an exception in training the child to use the right hand in eating, since this avoids later social discomfort. No measures more energetic than persistent encouragement in the use of the right hand for eating are justified.

TRAUMA AND PRIAPISM

To the Editor:—I have a case of priapism which I believe is on the basis of trauma and thrombophlebitis of the corpora cavernosa and spongeosum. The patient was injured about two weeks ago while attempting intercourse while under the influence of alcohol. The priapism came on at once and has existed up to the present. Neurologic consultation has ruled out cord lesion, the Kahn reaction is negative, and blood studies rule out a leukemia. Free use of sedatives and narcotics have failed to influence the condition, as have spinal anesthesia, high voltage roentgen therapy and diathermy. The therapeutic measure of greatest value to date has been sitz baths. I would appreciate any suggestions as to the diagnosis or treatment. M.D., Pennsylvania.

ANSWER.—There is no doubt from the history of the case that it belongs to the traumatic group. The treatment should be incisions under absolute asepsis to remove any blood clots and to allow free drainage of the exudate. The incisions should be made into the most turgid portions of the penis.

Medical Examinations and Licensure

COMING EXAMINATIONS

STATE AND TERRITORIAL BOARDS

ALABAMA: Montgomery, June 20-22. Sec., Dr. J. N. Baker, 517 Dexter Ave., Montgomery.

ARKANSAS: *Medical (Regular).* Little Rock, Nov. 3-4. Sec., State Medical Board of the Arkansas Medical Society, Dr. L. J. Kosminsky, Texarkana. *Medical (Eclectic).* Little Rock, Nov. 3. Sec., Dr. Clarence H. Young, 1415 Main St., Little Rock. *Basic Science.* Little Rock, Nov. 7. Sec., Mr. Louis E. Gebauer, 701 Main St., Little Rock.

CALIFORNIA: *Written examination.* Sacramento, Oct. 17-20. *Reciprocity.* Los Angeles, Nov. 16. Sec., Dr. Charles B. Pinkham, 420 State Office Bldg., Sacramento.

COLORADO: Denver, Oct. 5-7. Sec., Dr. Harvey W. Snyder, 831 Republic Bldg., Denver.

CONNECTICUT: *Basic Science.* New Haven, Oct. 8. *Prerequisite to license examination.* Address State Board of Healing Arts, 1895 Yale Station, New Haven. *Medical (Regular).* Hartford, Nov. 8-9. Sec., Dr. Thomas P. Murdock, 147 W. Main St., Meriden. *Medical (Homeopathic).* Derby, Nov. 8-9. Sec., Dr. Joseph H. Evans, 1488 Chapel St., New Haven.

DELAWARE: Dover, July 11-13. Sec., Medical Council of Delaware, Dr. Joseph S. McDaniel, 229 S. State St., Dover.

DISTRICT OF COLUMBIA: *Basic Science.* Washington, Dec. 26-27. *Medical.* Washington, Jan. 9-10. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA: Jacksonville, Nov. 14-15. Sec., Dr. William M. Rowlett, Box 786, Tampa.

GEORGIA: Atlanta, Oct. 11-12. Joint-Sec., State Examining Boards, Mr. R. C. Coleman, 111 State Capitol, Atlanta.

HAWAII: Honolulu, Oct. 10-13. Sec., Dr. James A. Morgan, 48 Young Bldg., Honolulu.

IDAHO: Boise, Oct. 4-5. Commissioner of Law Enforcement, Hon. J. L. Balderston, 205 State House, Boise.

ILLINOIS: Chicago, Oct. 18-20. Superintendent of Registration, Department of Registration and Education, Mr. Homer J. Byrd, Springfield.

INDIANA: Indianapolis, June 20-22. Sec., Board of Medical Registration and Examination, Dr. J. W. Bowers, 301 State House, Indianapolis.

IOWA: *Basic Science.* Des Moines, Oct. 11. Corres. Sec., Mr. H. W. Grefe, Capitol Bldg., Des Moines.

KANSAS: Topeka, Dec. 13-14. Sec., Board of Medical Registration and Examination, Dr. J. F. Hassig, 905 North 7th St., Kansas City.

KENTUCKY: Louisville, Dec. 6-8. Sec., State Board of Health, Dr. A. T. McCormack, 620 S. Third St., Louisville.

MAINE: Portland, Nov. 8-9. Sec., Board of Registration of Medicine, Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Medical (Regular).* Baltimore, Dec. 13-16. Sec., Dr. John T. O'Mara, 1215 Cathedral St., Baltimore. *Medical (Homeopathic).* Baltimore, Dec. 13-14. Sec., Dr. John A. Evans, 612 W. 40th St., Baltimore.

MASSACHUSETTS: Boston, Nov. 8-10. Sec., Board of Registration in Medicine, Dr. Stephen Rushmore, 413-F State House, Boston.

MICHIGAN: Lansing, Oct. 12-14. Sec., Board of Registration in Medicine, Dr. J. Earl McIntyre, 202-3-4 Hollister Bldg., Lansing.

MINNESOTA: *Basic Science.* Minneapolis, Oct. 4-5. Sec., Dr. J. Charnley McKinley, 126 Millard Hall, University of Minnesota, Minneapolis. *Medical.* Minneapolis, Oct. 18-20. Sec., Dr. Julian F. Du Bois 350 St. Peter St., St. Paul.

MISSISSIPPI: *Reciprocity.* Jackson, December. Asst. Sec., State Board of Health, Dr. R. N. Whitfield, Jackson.

MISSOURI: Kansas City, Oct. 18-20. State Health Commissioner, Dr. Harry F. Parker, State Capitol Bldg., Jefferson City.

MONTANA: Helena, Oct. 4. Sec., Dr. S. A. Cooney, 216 Power Block, Helena.

NEBRASKA: *Basic Science.* Lincoln, Oct. 4-5. *Medical.* Lincoln, Nov. 25-26. Dir., Bureau of Examining Boards, Mrs. Clark Perkins, State House, Lincoln.

NEVADA: Carson City, Nov. 7-9. Sec., Dr. John E. Worden, Capitol Bldg., Carson City.

NEW JERSEY: Trenton, Oct. 18-19. Sec., Dr. James J. McGuire, 28 W. State St., Trenton.

NEW MEXICO: Santa Fe, Oct. 10-11. Sec., Dr. Le Grand Ward, 135 Palace Ave., Santa Fe.

NORTH CAROLINA: *Reciprocity.* December. *Examination.* Raleigh, June 19. Sec., Dr. William D. James, The Hamlet Hospital, Hamlet.

NORTH DAKOTA: Grand Forks, Jan. 3-6. Sec., Dr. G. M. Williamson, 4½ S. Third St., Grand Forks.

OKLAHOMA: *Basic Science.* Oklahoma City, Nov. 30. Sec. of State, Hon. Frank C. Carter, State Capitol Bldg., Oklahoma City. *Medical.* Oklahoma City, Dec. 14. Sec., Dr. James D. Osborn Jr., Frederick.

OREGON: *Medical.* Portland, Oct. 5. Sec., Dr. Joseph F. Wood, 509 Selling Bldg., Portland. *Basic Science.* Portland, Nov. 19. Sec., State Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene.

PENNSYLVANIA: Philadelphia, January. Sec., Board of Medical Education and Licensure, Dr. James A. Newpher, 400 Education Bldg., Harrisburg.

RHODE ISLAND: Providence, Oct. 6-7. Chief, Division of Examiners, Mr. Robert D. Wholey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: Columbia, Nov. 8. Sec., Dr. A. Earle Boozer, 505 Saluda Ave., Columbia.

SOUTH DAKOTA: Pierre, Jan. 17-18. Director of Medical Licensure, Dr. B. A. Dyar, State Board of Health, Pierre.

VERMONT: Burlington, Feb. 14. Sec., Board of Medical Registration, Dr. W. Scott Nay, Underhill.

VIRGINIA: Richmond, Dec. 14-16. Sec., Dr. J. W. Preston, 30½ Franklin Road, Roanoke.

WEST VIRGINIA: Bluefield, Oct. 31-Nov. 2. Sec., Public Health Council, Dr. Arthur E. McClue, State Capitol, Charleston.

WISCONSIN: Madison, Jan. 10-14. Sec., Dr. Henry J. Gramling, 2203 S. Layton Blvd., Milwaukee.

WYOMING: Cheyenne, Oct. 3. Sec., Dr. G. M. Anderson, Capitol Bldg., Cheyenne.

NATIONAL BOARD OF MEDICAL EXAMINERS SPECIAL BOARDS

Examinations of *Special Boards* were published in THE JOURNAL, September 24, page 1235.

Texas June Examination

Dr. T. J. Crowe, secretary, Texas State Board of Medical Examiners, reports the written examination held at San Antonio, June 20-22, 1938. The examination covered twelve subjects and included 120 questions. An average of 75 per cent was required to pass. One hundred and ninety-two candidates were examined, 176 of whom passed and sixteen failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Rush Medical College		(1937)	76.7
School of Med. of the Division of Biological Sciences		(1935)	84
Tulane University of Louisiana School of Medicine		(1931)	81.6
Harvard Univ. Medical School	81, (1934) 84.3,	(1936)	84.6
Creighton University School of Medicine		(1937)	84.5
Columbia Univ. College of Physicians and Surgeons		(1938)	82
University of Oklahoma School of Medicine		(1938)	77.6
University of Pennsylvania School of Medicine		(1938)	81
Baylor University College of Medicine	79, 85, (1938) 75.4, 75.5 75.5, 76.8, 78, 78, 78.9, 79, 79, 79, 79, 79.8, 79.9, 80, 80.4, 80.4, 80.6, 80.9, 81, 81, 81.2, 81.4, 81.5, 81.5, 81.6, 81.8, 81.9, 82, 82.1, 82.1, 82.3, 82.5, 82.7, 83, 83, 83, 83.1, 83.2, 83.2, 83.5, 83.6, 84, 84, 84.2, 84.2, 84.2, 84.3, 84.5, 84.6, 85, 85, 85, 85, 85, 85.1, 85.2, 85.3, 85.3, 85.6, 86, 86, 86.1, 86.3, 86.5, 86.5, 86.6, 86.7, 86.9, 89, 89.4, 91	(1937)	76.9,
University of Texas School of Medicine	(1938) 76.6, 77.3, 77.6, 78.4, 78.4, 78.5, 79.3, 79.3, 79.5, 79.5, 79.9, 80, 80, 80, 80, 80.3, 80.3, 80.4, 80.5, 80.5, 80.7, 80.7, 80.8, 80.8, 81, 81, 81.1, 81.2, 81.2, 81.2, 81.3, 81.4, 81.4, 81.4, 81.5, 81.8, 81.9, 81.9, 81.9, 82, 82, 82.1, 82.3, 82.3, 82.3, 82.5, 82.5, 82.7, 82.9, 82.9, 83, 83, 83.3, 83.5, 83.9, 84, 84.5, 84.5, 84.8, 84.8, 85.4, 85.6, 85.7, 86, 86.1, 86.3, 86.3, 86.5, 86.6, 86.6, 87.5, 88.1	(1937)	81.7,
McGill University Faculty of Medicine		(1938)	75.6
Osteopaths*	76.5, 77, 77, 77.7, 77.7, 78.9, 79.1, 80.2, 80.3, 81.1, 81.2, 81.4, 81.5,† 82.6, 82.8, 83.6, 85.4		75.3,

School	FAILED	Year Grad.	Number Failed
University of Arkansas School of Medicine		(1937)	1
Creighton University School of Medicine		(1936)	1
Baylor University College of Medicine		(1938)	1
University of Texas School of Medicine		(1938, 3)	3
Osteopaths*			10

One hundred and six applicants were licensed by reciprocity and one applicant was licensed by endorsement on July 30. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
University of Arkansas School of Medicine	(1932), (1935), (1936), (1937, 4), (1938)		Arkansas
College of Medical Evangelists		(1931)	California
University of Colorado School of Medicine	(1925), (1937)		Colorado
University of Georgia Medical Department		(1924)	New York
University of Georgia School of Medicine		(1934)	Georgia
Chicago College of Medicine and Surgery		(1911)	Indiana
Loyola University School of Medicine		(1934)	Illinois, Indiana
Northwestern University Medical School	(1916), (1921) (1923)		Kansas, (1934, 2) Wisconsin, (1935) Michigan
University of Illinois College of Medicine		(1925)	Illinois
State University of Iowa College of Medicine		(1928)	Iowa
University of Kansas School of Medicine	(1925), (1926), (1936), (1937)		Kansas
Kentucky School of Medicine		(1904)	Oklahoma
Kentucky University Medical Department		(1906)	Kentucky
Louisiana State University Medical Center	(1936) (1937), (1938, 2)		Georgia, Louisiana
Tulane University of Louisiana Medical Department		(1912)	Louisiana
Tulane Univ. of Louisiana School of Medicine	(1928), (1931) (1932)		Alabama, (1936, 5), (1937, 5) Louisiana, Mississippi,
Harvard University Medical School		(1935)	Maine
Univ. of Michigan Dept. of Medicine and Surgery		(1910)	Michigan
University of Michigan Medical School	(1931) (1933)		New York, (1928), (1931), (1937) Michigan, Minnesota,
Univ. of Minnesota Medical School	(1933)		Minnesota, (1935) Illinois
Barnes Medical College, Missouri		(1902)	Illinois
University of Nebraska College of Medicine	(1929) (1933), (1937)		Kansas, Nebraska
Cornell University Medical College		(1934)	New York
University of Buffalo School of Medicine		(1929)	New York
Duke University School of Medicine		(1935)	Maryland
Ohio State University College of Medicine	(1921), (1937)		Ohio
University of Oklahoma School of Medicine	(1933), (1934), (1935), (1936)		Oklahoma
Hahnemann Med. College and Hospital of Philadelphia	(1936)		Penna.
Jefferson Medical College of Philadelphia		(1921)	Ohio
University of Pittsburgh School of Medicine		(1909)	Penna.
Meharry Medical College		(1937)	Tennessee
University of Tennessee College of Medicine	(1930) (1928), (1936, 2), (1937, 2)		Mississippi, Tennessee
Vanderbilt University School of Medicine	(1913) (1933), (1937)		Illinois, Tennessee

Baylor University College of Medicine	(1937)	Louisiana
Medical College of Virginia	(1937)	Virginia
University of Virginia Department of Medicine	(1932)	Virginia
Marquette University School of Medicine	(1913)	Wisconsin
McGill University Faculty of Medicine	(1935)	Washington
Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau	(1934)	New York
Osteopaths‡ Arkansas, Indiana, Iowa, 5, Kansas, Michigan, Missouri, Oklahoma, 5, South Dakota, Virginia		

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
University of Pennsylvania Department of Medicine		(1898)	U. S. Army

* Examined in medicine and surgery.
† License has not been issued.
‡ Licensed to practice medicine and surgery.

Book Notices

Industrial Surgery: Principles, Problems and Practice. By Willis W. Lasher, M.D., F.A.C.S., Assistant Professor of Traumatic Surgery, New York Post-Graduate Medical School, Columbia University, New York. Cloth. Price, $6. Pp. 452, with 193 illustrations. New York: Paul B. Hoeber, Inc., 1938.

The wide scope in industrial surgery, which is only one department of industrial medical practice, is illustrated by the table of contents in this new work. The author states that there is scarcely a part of the human body which is not subject to the effects of trauma nor are there any tissues which have not become secondarily invaded by the complications associated with injury. Lasher's wide experience in industrial accidents serves as a basis for a comprehensive review of this field of surgery, with excellent chapters on general surgical considerations including a discussion of embryology, histology, physiology, biochemistry and surgical pathology. In developing his book the author has confined himself to his actual experiences and has not attempted to bridge over omissions by referring to other sources. In the preface the philosophy of industrial surgery is discussed and a sound approach to the various problems encountered is indicated which is well carried out throughout the text. The book includes chapters on the organization of medical departments in industry, an appendix describing various appliances used by the author, and a fairly complete bibliography. It should prove a valuable working manual in this field.

Endogene Endokrinotherapie in der Gynäkologie: Ätiologie und Behandlung des Karzinoms. Von Dr. Jules Samuels, Chirurg-Frauenarzt, Leiter der Einrichtung für Kurzwellentherapie, Amsterdam. Paper. Price, 4.90 florins. Pp. 182, with 32 illustrations. Leiden: A. W. Sijthoff's Uitgeversmaatschappij N. V., 1938.

During the last two years the author of this book has written three books and twenty-five articles, and the latter were published in Netherland, German, French, British, American, Italian and Japanese journals. These books and articles dealt almost exclusively with one subject. The author devised an instrument which he calls a cycloscope, the essential part of which is a spectroscope. He uses the instrument to study the endocrine glands and plots curves which he calls cyclograms. He makes many remarkable statements which have not as yet been substantiated by others. Some of these contentions are the following: Women ovulate two or three times a month and therefore can become pregnant this often during each intermenstrual interval. The author can tell by means of his instrument exactly which endocrine gland has a disturbed function and whether there is excessive or diminished hormonal activity of this gland. Likewise he can tell whether the dysfunction can be remedied or not. He can cure heretofore incurable endocrine disturbances by means of short wave therapy. He can successfully treat a dysfunctioning pituitary gland and in this way indirectly treat the mesencephalon and diencephalon. Duodenal and gastric ulcers have a central origin and the dysfunctioning of the stomach center is caused by a gonadotropic hyperpituitarism. Climacteric disturbances are due to dysfunctioning of the diencephalus under the influence of overproduction of gonadotropic hormone. The toxemias of pregnancy are due to hyperproduction of placental hormone, especially the placental estrogenic hormone. Many cases of genuine liver and kidney disease have a hormonal origin, which consists of a hyperfunction of the gonadotropic hormones the result of a gonadotropic hyperpituitarism. Habitual abortion is due to hypoproduction of placental hormone, thereby enabling its antagonist, the posterior pituitary hormone, to act. Likewise hydatid moles have their origin in hypoproduction of placental estrogenic hormone. In cases of benign tumors there is always a gonadotropic hyperpituitarism and in cases of malignant tumors there is a thyrotropic hyperpituitarism. Therefore the endocrine electrodiagram is a helpful means of differentiating a benign from a malignant tumor. In the management of tumors, the pituitary must be treated. The most efficient way of treating carcinoma endocrinologically is to apply short wave therapy to the pituitary and to the gonads except in cases in which the gonads are already inactive. In such cases, treatment of the pituitary alone suffices. The author ends his book with the statement that the cycloscope is an indispensable instrument. However, thus far no one has published any confirmatory evidence in support of the author's contentions. In one large university in this country the cycloscope has failed completely to substantiate what Samuels claims for it.

The Synovial Membrane and the Synovial Fluid with Special Reference to Arthritis and Injuries of the Joints. By David H. Kling, M.D., Assistant Professor of Orthopedic Surgery and Chief of Arthritis Clinic, White Memorial Hospital, Los Angeles, California. Cloth. Price $5. Pp. 299, with 80 illustrations. Los Angeles: Medical Press, 1938.

Few medical schools give instruction on the diagnostic and prognostic value of synovial fluid, in contrast to the emphasis placed on the cerebrospinal fluid. With the publication of Kling's readable monograph there is no longer any excuse for omitting consideration of the synovial fluid as actually and potentially as important as the spinal fluid. The present knowledge of the histogenesis, morphology and functions of the synovial membrane and its physiology are ably reviewed. The author has himself been one of the principal investigators in the field. Also the pathologic alterations of the synovial membrane in disease are discussed. This consideration of the synovial membrane is a necessary preliminary to accurate knowledge of the origin and function of synovial fluid and meaning of changes in this fluid as a reflection of the pathologic conditions. The monograph closes with four brief chapters on the clinical value of the aspiration of joint effusions and the technic and value of aspiration as a diagnostic procedure either alone or combined with injection of liquids and gases and their therapeutic usefulness. There are still many features of the synovial membrane and synovial fluid the exact significance of which is not yet determined. These holes in knowledge and interpretation are, however, rapidly filling, as can be determined by the number of recent references contained in the book. Furthermore the deficiencies in knowledge are not so large as to discourage the more widespread adoption of articular aspirations and further clinical pathologic studies. This monograph can be considered the most authoritative book in its field available today and it is hoped that the author will revise it at frequent intervals, since progress is so rapid that many of the hiatuses in knowledge may not remain unfilled for long.

Diseases of the Thyroid, Parathyroids and Thymus. By André Crotti, M.D., F.A.C.S., LL.D., Surgical Assistant at Roux's Clinic, Lausanne, Switzerland. Third edition. Leather. Price, $20. Pp. 1,229, with 301 illustrations. Philadelphia: Lea & Febiger, 1938.

This edition closely resembles the previous edition in the luxuriousness of the makeup and the inevitable ribbon marker. The contents of the book have been enlarged by the addition of a chapter on the fundamental physiology and pathology of the parathyroid glands. The author freely injects his own ideas about the function of these glands and their various relationships to other organs and tissues of the body. Many of his conclusions are empirical and abrupt, presented in a staccato manner without sufficient discussion. Others are long and involved, fortified with case histories and reports of experimental studies; all statements seem overwhelmingly and equally positive. Endemic goiter is attributed to a fungus found in cabbage. The author cites some experimental proof of this according to his observations and claims to have fulfilled Koch's postulates. There is a great deal of information in this book which could have been

digested and presented in a much briefer content. The bibliography is complete but is presented at the back of the book without annotation, thus losing much of its value. The index is excellent, but the tyro in thyroid disease would soon lose himself in the maze. A research worker in thyroid disease would find this volume interesting if only because of the author's wide and long experience.

Health Education of the Public: A Practical Manual of Technic. By W. W. Bauer, B.S., M.D., Director, Bureau of Health and Public Instruction, American Medical Association, and Thomas G. Hull, Ph.D., Director, Scientific Exhibit, American Medical Association. Cloth. Price, $2.50. Pp. 227, with 39 illustrations. Philadelphia & London: W. B. Saunders Company, 1937.

This practical manual of technic of health education of the public sets forth in detail the various means of health education at the disposal of the health officer, the medical society or the individual physician. It shows clear understanding of these methods and, while it explains them simply, they are discussed thoroughly. The authors first point out some of the sources of material for the health educator: books, magazines, health agencies, federal and local, and medical colleges and universities, with various lists of agencies where information can be obtained. The authors then evaluate the various means of disseminating this health information: the radio, the exhibit, the meeting, pamphlets, the newspaper, the motion picture, stereopticon slides, the magazine article, correspondence, books and miscellaneous devices, such as the healthmobile. They discuss each of these methods to determine how each of them can be used most effectively and they also give a list of subjects that may be used for timely talks. Every health educator should have a copy of this manual at hand for reference purposes.

Approved Laboratory Technic: Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical and Histological. By John A. Kolmer, M.D., Dr.P.H., Sc.D., Professor of Medicine, Temple University, Philadelphia, and Fred Boerner, V.M.D., Assistant Professor of Bacteriology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, Philadelphia. Second edition. Cloth. Price, $8. Pp. 893, with 392 illustrations. New York & London: D. Appleton-Century Company, 1938.

As the title indicates, this edition was prepared under the auspices of the American Society of Clinical Pathologists. Each chapter has been revised and five new chapters have been added. These cover the subjects which have assumed importance in the seven years since publication of the first edition. Special emphasis is given to parasitology. The chapter on tissues also includes directions for the preparation of museum specimens. The most reliable methods and only those tests of approved value are given. The text is clear and concise; the procedures are definite and leave nothing to the imagination. Clinical pathologists, medical technicians and physicians performing laboratory tests will find this book not only a valuable one to own but the most reliable one to consult.

A Survey of Chronic Rheumatic Diseases Contributed by Contemporary Authorities in Commemoration of the Bicentenary of the Royal National Hospital for Rheumatic Diseases, Bath, 1738-1938. Compiled under the direction of the following Editorial Committee: R. G. Gordon, M.D., D.Sc., F.R.C.P., Chairman, G. P. R. Aldred-Brown, M.A., D.M., J. Barnes Burt, M.D., F. J. Poynton, M.D., F.R.C.P., R. Waterhouse, M.D., F.R.C.P., and G. D. Kersley, M.D., M.R.C.P., Secretary. Cloth. Price, $6.50. Pp. 338, with illustrations. New York, Toronto & London: Oxford University Press, 1938.

This volume is issued to commemorate the bicentenary of the founding of the Royal Mineral Water Hospital at Bath. Its aim is to survey the current knowledge of rheumatic diseases. In pursuit of this purpose, recognized students of rheumatism from many lands have contributed chapters on different aspects of these diseases. Following a brief foreword reviewing some of the history of the Royal Mineral Water Hospital and its contributions to the country, especially in time of war, the book opens with a scholarly chapter on the history of chronic rheumatism by Sir Humphry Rolleston. While of necessity the discussion touches only the high spots, it serves as an excellent introduction to the subject. The French "concept of 'arthritisme'" is contributed in a chapter by Bezançon and Weil; a chapter on the osteo-arthritic syndrome by Polak of Paris is included. Professor Kahlmeter of Stockholm contributes an excellent chapter on the sedimentation rate in arthritis, and Lindstedt of the same city on the pathogenesis and etiology of sciatica. The United States is ably represented in the excellent chapter by Hench on whether rheumatoid (atrophic) arthritis is a disease of microbic origin, one on the pathology of nonspecific arthritis by Ghormley, and chapters by Pemberton and Scull and by Osgood. Freund of Vienna has a chapter on the importance of biochemistry in the investigation of rheumatic diseases, and Aschoff of Freiburg on allergy in arthritis. Although most of the other chapters are, of course, written by eminent Englishmen, Van Dam of Amsterdam has one on radiography in rheumatism and the volume closes with one on organization and treatment of chronic rheumatism by Professor Van Breemen of Amsterdam. In spite of the multiplicity of authorship, the book is more than a collection of essays. It constitutes in its entirety a broad gage discussion of the present state of knowledge in many aspects of rheumatic diseases. No one, beginner or specialist, could fail to read it without obtaining much that is both informative and thought provoking.

Life and a Living: Report of the Committee for the Care of the Jewish Tuberculous, 1913-1936. Paper. Pp. 65, with illustrations. New York, [n. d.]

This report of the Committee for the Care of the Jewish Tuberculous deals with the care and rehabilitation of the tuberculous patient after graduation from the sanatorium. Through the Altro workshops, operated by the committee, the convalescent tuberculous person is given opportunity for paid employment. Easy jobs, light work or part time jobs are not always to be found. Employers still hesitate to place the ex-tuberculous among their apparently healthy employees for fear of infection. Hence the ex-tuberculous person finds it doubly hard to become self supporting. The aim of the Altro workshop as described in this report is to restore as far as possible the worker to his place in the community. This is not the only object of the rehabilitation program by this committee, as the committee points out that by its program it reduces materially the relapses among the patients discharged from the sanatorium. This booklet will be of value to the physician who has an interest in the problem of the ex-tuberculous in industry. Mention is made of similar projects in England, but no word is found of other like endeavors in this country.

Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats: A Neurotropic Factor in Wheat Germ Oil. By Lárus Einarson, M.D., Professor of Anatomy, and Director of the Institute of Anatomy, University of Aarhus, Denmark, and Axel Ringsted, M.D., Assistant at the University Institute of Hygiene and the State Vitamin Laboratory, Copenhagen. Translated from Danish by Hans Andersen, M.D. Paper. Pp. 163, with 97 illustrations. Copenhagen: Levin & Munksgaard; London: Oxford University Press, 1938.

The first part of this monograph describes the clinical manifestations of neuropathic disturbances that develop in adult rats on a diet without vitamin E. These disturbances are prevented under certain conditions by a factor in wheat germ oil. The second part is devoted to a careful description of the extensive anatomic changes that may develop in the nervous system and skeletal muscles of adult rats fed without vitamin E. Whether the neurotropic principle in wheat germ oil is identical with vitamin E is not fully decided, but the facts at hand indicate that the two are identical.

The Chemistry of Antigens and Antibodies. By J. R. Marrack. Medical Research Council, Special Report Series, No. 230. Paper. Price, 3s. Pp. 194, with 27 illustrations. London: His Majesty's Stationery Office, 1938.

This report is a revised edition of report 194, published in 1935 under the same title. The usefulness of the earlier report indicated the need of revision in order to include the many important results of the work during the last few years on the chemistry of antigens and antibodies. The first chapter discusses such fundamental matters as the shapes and sizes of molecules, intermolecular (polar) forces, the structure of proteins and the stability of suspensions with special reference to antigen-antibody reactions. Then comes a consideration of the nature of antibodies, mainly from the point of view of their relation to proteins. The special topics considered are the

separation of antibodies from other serum constituents, the stability of antibodies, the antigen-antibody complex, the relation of antibody globulin to normal globulin, and the increase of serum proteins on immunization. The third chapter deals with the specificity of antigens, including artificial and natural protein antigens, polysaccharides and lipins. The last two chapters take up the nature of the antigen-antibody reaction, which is divided into two stages, specific combination and secondary reaction. At the end of each chapter is a list of appropriate references. There is a complete index. The first edition contained 135 pages. A work of great interest and usefulness to all students of pathogenic organisms and immunology has been brought well and thoroughly abreast of the times.

Actinomycosis. By Zachary Cope, B.A., M.D., M.S., Surgeon to St. Mary's Hospital, Paddington. Cloth. Price, $5.50. Pp. 248, with 60 illustrations. New York, London & Toronto: Oxford University Press, 1938.

According to the author, this is the first monograph on actinomycosis in English. The first six chapters deal with general aspects of the disease: definition and history, characteristics of actinomyces, incidence, clinical features, diagnosis, prognosis and treatment. The history of the infection, the characteristics of the organism, the incidence, the general clinical features, the diagnosis, prognosis and treatment of the disease are considered as well as its localizations in different organs and tissues. There is a selected bibliography, an index of names and a subject index. Most of the illustrations are borrowed from older publications and many are now mainly of historical interest. Eight are in color. The monograph summarizes conveniently the knowledge of actinomycosis but it does not say anything about the disease that has not been said before.

Maternal Care Complications: The Principles of Management of Some Serious Complications Arising During the Antepartum, Intrapartum, and Postpartum Periods. Approved by the American Committee on Maternal Welfare, Inc. Prepared by R. D. Mussey, M.D., P. F. Williams, M.D., and F. H. Falls, M.D., F. L. Adair, M.D., Editor. Cloth. Price, $1. Pp. 95. Chicago, Illinois: University of Chicago Press, 1938.

This booklet was written because of the enthusiastic response to the monograph which was published last year by the American Committee on Maternal Welfare, Inc., under the title "Maternal Care." The second volume presents the essential facts concerning the three major causes of maternal mortality, namely the toxemias of pregnancy, hemorrhages and puerperal infection. The three chapters were prepared by R. D. Mussey, P. F. Williams and F. H. Falls respectively. The second volume, like the first, should be carefully read and reread by every physician who practices obstetrics. If the general practitioners of this country were to learn the principles enumerated in this book and apply them to the best of their ability, there would be considerably less cause for worry about maternal and fetal death rates which exist at present. Every physician who cares for obstetric patients should possess a copy of this book.

An Introduction to Clinical Scotometry. By John N. Evans, M.D., F.A.C.S., Professor of Clinical Ophthalmology, Long Island College of Medicine. Published for Long Island College of Medicine. Cloth. Price, $4. Pp. 266, with 57 illustrations. New Haven: Yale University Press; London: Oxford University Press, 1938.

This scientific monograph represents a compilation of study and material that the author has accumulated during the past nine years and is an effort to bring together the evidence from various sources so that it may be more available than in its present widely disseminated form in the periodical literature. In the fourteen main chapters he traces the history of plotting the central field of vision from the early part of the seventeenth century down to the present highly technical method of angioscotometry that he has developed and perfected. The necessary equipment, the technic, the application to clinical conditions and the theoretical considerations involved in central field work are described in sufficient but not unnecessary detail. There are enough illustrations to emphasize the desired points. The by-paths of angioscotometry are considered in the various appendixes and to round it out there is a working bibliography of 320 references. As the name of Evans is intimately associated with angioscotometry, it must be stated emphatically that the book is not given over to the highly scientific but clinically unpractical plotting of the retinal vessels but deals rather with the clinical scotomas of the central visual field. Consequently the volume should have a definite place in the library of every modern ophthalmic clinician.

Structural Variations of the Human Iris and Their Heredity With Special Reference to the Frontal Boundary Layer. By Viggo Eskelund, M.D. Paper. Price, 21s. Pp. 243, with illustrations. Copenhagen: Nyt Nordisk Forlag, Arnold Busck; London: H. K. Lewis & Co., Ltd., 1938.

This monograph deals with the structural variations of the iris and to a lesser extent the cornea. The author endeavors to classify the variations in his own inimitable manner, with a view to establishing the limit of the structural variations, their mutual relation and their frequency. The photographic examinations of the anterior surface of the iris were carried out on hundreds of patients and the endeavor was made to trace a hereditary relationship in the contour of the various aspects of the anterior iris. This was successful in only a limited percentage, corresponding to the earlier investigation of Weninger. Forty-four iris photographs, enlargements of Graflex prints, are reproduced. In the majority of instances the individual iris markings are badly blurred and this is increased by corneal reflex of the photo-flash lamp that was used for illumination. The photographs could not be called an unmitigated success. The last eighty-four pages of the monograph are devoted to an analysis of the patients, numbering well over 160. With each case is given the Bertillon-like formula of structure of the iris. However, the endeavor to classify human beings by the forms of the iris, similar to the classification by the form of the finger prints, is not a success. Neither is the relationship of iris structure sufficiently accurate to permit of recognition of paternity. The monograph is closed with a short bibliography. The enormous amount of work represented by this book must be available to interested research workers in libraries, but it is not worth a place in the library of a practical ophthalmologist.

The Pharmacological Shock Treatment of Schizophrenia. By Dr. Manfred Sakel. With a foreword by Professor Otto Pötzl, Chief of the University Clinic for Neurology and Psychiatry of Vienna, Austria. Authorized translation by Joseph Wortis, M.D., Research Fellow at the Bellevue Psychiatric Hospital of New York. Enlarged version of a series of articles from the Wiener medizinische Wochenschrift, 1934-35. Nervous and Mental Disease Monograph Series No. 62. Cloth. Price, $2.75. Pp. 136, with illustrations. New York & Washington: Nervous and Mental Disease Publishing Company, 1938.

The book presents in convenient form Sakel's method of the insulin treatment of schizophrenia. The procedure is clearly outlined and many suggestions are made which will be helpful to the practitioner. Emphasis is laid on individualizing the procedure in different cases, but the criteria which decide at what phase the treatment should be interrupted are vague. A number of case histories are critically discussed. Sakel undoubtedly deserves credit for showing that schizophrenia can be "cured" by a treatment involving definite physiologic changes in the brain, but his attempts to account for them are unscientific. It seem to be regrettable that a book that is bound to be read by psychiatrists all over the country contains passages such as "The action of insulin therefore consists in: (1) neutralization of the excitant hormone and (2) vagotonic muffling of the cell." Investigations of other authors on the insulin treatment are almost completely omitted.

Surgical Handbook for Hospital Assistants in the Tropics. By W. E. Connell, M.B., Ch.B., F.R.C.S., Surgical Specialist, Tanganyika Territory. Cloth. Price, 12s. 6d. Pp. 440, with 177 illustrations. London: John Bale Medical Publications, 1938.

The problems presented in this book have no interest for medical practitioners in general. Army medical officers, especially in the tropics, might find this small volume instructive in the training of the orderly. The problems presented are peculiar to the British tropical service with its experience with native dispensers. Because of the quasimedical nature of its audience, presentation is dogmatic and brief. This is a dangerous policy, since duties seem to extend beyond first aid into the realm of diagnosis and treatment, which always require competent medical care.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Damages: Paralysis Following Cerebral Hemorrhage Mistaken for Drunkenness.—The plaintiff, a minister of the gospel, was a passenger on a bus operated by the Tri-State Transit Company. When the bus arrived at its destination the driver observed that the minister remained in his seat, apparently asleep, and attempted to arouse him. He was unable to do so and, thinking that the man was drunk, he called a helper and the two lifted the minister bodily from the seat in the bus, carried him into the waiting room of the station, put him in a chair, and left him. A short time thereafter, an outsider went into the waiting room and saw the minister lying prostrate on the floor. The ticket agent for the transit company, on being informed by this outsider of the supposed drunken condition of the minister, telephoned police headquarters stating that there was a drunken man at the station lying on the floor and asked that some one be sent to take charge of him. Two policemen who came in response to the call assumed, too, that the minister was drunk, carried him to police headquarters, entered a charge of drunkenness against him and locked him up. Apparently no further attention was paid to him until about twenty-four hours later, when the city physician was notified and immediately discovered that the minister had suffered a cerebral hemorrhage which had almost completely paralyzed him and rendered him speechless. A brother of the minister, summoned from a distance of about 100 miles, came and took charge of him. While at the time of the trial the minister's condition had considerably improved, he was still paralyzed and totally incapacitated. He brought suit against the Tri-State Transit Company and the Interurban Transportation Company for damages. The trial court's judgment for the defendants was affirmed by the court of appeals and the plaintiff appealed to the Supreme Court of Louisiana.

The Interurban Transportation Company was absolved from liability because the evidence showed that it had no contractual relationship with the plaintiff, who intended to continue his journey over that bus line but had purchased no ticket. The Supreme Court was of the opinion that the plaintiff had failed to make out his case against the remaining defendant, so far as he claimed damages for permanent and total disability. According to the testimony of physicians, it was not at all likely that medical attention, if administered immediately after the plaintiff suffered the stroke, would have averted the paralysis. In their opinion the paralysis which totally disabled the plaintiff would in any event have followed the stroke.

The assumption of the employees of the bus company that the plaintiff's limp and helpless condition was due to drunkenness, said the court, was extremely far fetched. But assuming that they did so believe and that they acted in good faith, their mistake was the misfortune of the company, and it is liable for injuries sustained by the plaintiff by reason of that mistake. After observing that a passenger is helpless and unable to take care of himself, from whatever cause, it is the duty of a carrier's employees to exercise reasonable care and diligence to make at least temporary provisions for his protection and comfort. A failure to do so is clearly a violation of the contract for safe passage. Instead of performing the duty in the present case, it was assumed without the slightest foundation, in the opinion of the court, that the plaintiff was in a drunken stupor and the report was spread abroad that he was drunk. Although the plaintiff was paralyzed and utterly helpless, he was not unconscious. He realized what was going on but could not explain or call for help. Not the slightest attention was paid to him during the time he lay in jail on the concrete floor. To say nothing of the pain and suffering resulting from the stroke, the suffering he must have undergone from the discomfort of lying on the floor without ministration to his ordinary bodily needs, and the consciousness of his innocence and his utter inability to call for or to obtain help can well be imagined, the court said. He suffered some from the stroke itself. For this the carrier was not at fault. But the fact is that, if he had been afforded proper medical and other treatment, his discomfort and suffering would not have been so severe. For this item of damage, therefore, the court thought that the plaintiff should be awarded $2,500.

As to the slander charge, there was no testimony that the plaintiff's reputation as a minister was injured. His friends and parishoners did not believe the report that he was drunk. But in the opinion of the court he was entitled to nominal damages for the false and slanderous charges made against him. The court assessed his damage under this item at $1,000.

The judgments of the lower courts were therefore reversed and the Tri-State Transit Company was ordered to pay the plaintiff the sum of $3,500.—*Searcy v. Interurban Transp. Co., Inc., et al. (La.), 179 So. 75.*

Workmen's Compensation Acts: Traumatic Aggravation of Perthes' Disease.—The employee, in the course of his employment, slipped on a greasy floor and fell, with legs spread apart, on to his right hip and the lower part of his back. An examination by the company physician, made three days later, disclosed no swelling or discoloration of the parts of the hip and back where the employee complained of pain. Several days later the company physician again examined him and discovered a limitation of motion of his right leg. A roentgenogram revealed that the head of the femur in the right hip was flattened. The employee was paid compensation for a period of eight months, after which it was discontinued. Thereafter, he instituted proceedings to recover additional compensation. The industrial commission denied the application, finding that the employee was suffering from chronic Perthes' disease and that this, not the accident, was the cause of his disability. The employee appealed to the Supreme Court of Minnesota, predicating his right to recover additional compensation on the theory that the accident had aggravated the pre-existing Perthes' disease.

Perthes' disease, said the Supreme Court, has been recognized only within comparatively recent years. It has its genesis in childhood while the femur is in a formative state. Whether it results from infection or from trauma is disputed; but its effect, whatever the cause, is the flattening of the head and the broadening of the neck of the femur. Since the head of the femur thereby becomes maladjusted to the socket into which it is supposed to fit, some limitation of the normal movement of the leg necessarily results. After the initial flattening and broadening of the femur occurs, the condition may remain quiescent for many years, but during adult life it has been noted in some cases that chronic or degenerative arthritis later develops. In its more advanced state it is accompanied by pain, muscle spasm in the vicinity of the affected bone, and considerable limitation of movement of the leg. It may originate without the knowledge of the afflicted person; its resurgent activity after a period of quiescence has been said to be due to traumatism caused by the overuse of a mechanically imperfect joint. It was conceded by the employee that the flattened and broadened condition of the femur existed at the time of the accident. He was then 43 years of age and had been employed at heavy manual labor all his life. He had never been sick and could remember no accident which might have caused Perthes' disease during his youth. He claimed that this accident aggravated the condition of his femur and that since the accident he had suffered pain and muscle spasm in the area of his right hip, had been unable to stand on his feet for any considerable period, that the movement of his leg was limited and a limp had developed through the shortening of the right leg, and that there had been atrophy of the muscles of his right thigh. The physicians of his selection who examined and treated him following the accident substantiated his contention.

The medical witnesses called by the employer and those appointed by the industrial commission categorically denied the truth of the employee's assertions. They testified that the

roentgenograms taken soon after the accident, when compared with those taken two years later, failed to show the slightest change in the abnormal condition of the femur and that therefore there was no justification for an assumption that the condition of the femur differed in the slightest from its condition at the time of the fall. They maintained that the accident imposed a strain on the soft parts of the body on which the relator fell without affecting the femur, and that the period for which compensation was paid was ample to permit a recovery from those strains to the soft tissue. They admitted that the condition of the femur would impose some limitation on the movement of the leg, but contended that this limitation at the time of the trial was no more extensive than it was when the accident occurred.

The court could find in the evidence nothing to justify it in overruling the findings of the commission and the order disallowing compensation was affirmed.—*Henz v. Armour & Co. (Minn.), 277 N. W. 923.*

Accident Insurance: Death from Botulism as Death from "Bacterial Infection."—A life insurance policy containing a double indemnity clause provided that double indemnity was not payable if the insured's death resulted "from the taking of poison or . . . from any bacterial infection other than bacterial infection occurring in consequence of accidental and external bodily injury." It was admitted that the insured's death was due to botulism contracted through eating home-canned beans. The insurance company denied liability for double indemnity, contending that the death was due to "the taking of poison" or to "bacterial infection." The trial court gave judgment for the beneficiary, and the company appealed to the Supreme Court of Colorado.

Webster's New International Dictionary, said the court, defines infection to mean the "process of infecting" and the word "infect" to mean "to contaminate with a disease-producing substance, germs or bacteria." Technically, the court continued, the illness produced by bacteria themselves is referred to as infection, while that occasioned by the poison produced by such bacteria is referred to as poisoning. Gould's Dictionary of Medicine defines "botulism" as poisoning and defines "infection" as "the communication of disease-germs or virus by any means, direct or indirect." The same authority defines disease as "a condition of the body marked by inharmonious action of one or more of the various organs owing to abnormal condition or structural change." All of this, the court pointed out, merely reinforces and confirms the popular interpretation or commonly accepted meaning of bacterial infection as covering such afflictions as botulism, admittedly caused by the germ known as Bacillus botulinus. In the amended complaint the beneficiary contended "That said deceased on April 21, 1937, ate home canned beans containing Bacillus botulinus and then and there became infected with said bacillus." This statement was repeated in the stipulation of facts. The contentions, therefore, of the insurance company that death resulted from "bacterial infection" seemed to the court to be admitted by the beneficiary. Hence the exception contained in the insurance policy covered the case and the double indemnity clause was not applicable. The court, therefore, reversed the judgment of the trial court and remanded the case with instruction to enter judgment for the insurance company.—*New York Life Ins. Co. v. Mariano (Colo.), 76 P. (2d) 417.*

Evidence: Right of Physician Witness to Testify Concerning Probable Effect of Injury.—In the trial of a personal injury suit in which it was alleged that the plaintiff's left leg was fractured when he was struck by a car driven by the defendant, a physician called by the plaintiff was asked the cause of the pain from which the plaintiff testified he suffered. The physician stated that in his opinion it was caused by adhesions that tended to limit the function of the limb; that is, fibrous unions between two tissues resulting from inflammation. The physician was then asked whether in his opinion the conditions caused by the adhesions were likely to be permanent. Basing his answer on his observations of the tendons and the condition of the leg, on his own knowledge and on the history of the patient, the physician stated that the conditions were likely to be permanent and that with reasonable certainty the pain would continue permanently in the future. Another physician, who had taken roentgenograms of the plaintiff, when asked his opinion as to the cause of the pain in the region of the fractures after any sustained use of the leg, attributed it "to the atrophy of the muscles, to the shortening of both legs, to the angulation of the fragments and the change in the weight bearing line," which was impaired by reason of the bowing and angulation of the lower left leg. All this testimony was admitted over the objection of the defendant. From a judgment for the plaintiff the defendant appealed to the Supreme Court of Michigan.

The defendant contended that the testimony of the physician witnesses outlined above invaded the province of the jury and was therefore inadmissible. The Supreme Court, however, took a different view. A physician, said the court, may testify as to the extent of certain injuries, whether the injury is permanent or not, the probability of recovery, and the probable results of the injury. This, the court thought, did not come within the rule that excludes the opinion of a witness as to the ultimate fact that the jury is called on to determine. A medical man may testify as to his opinions concerning the condition of the human system, the probability of recovery from an injury and other matters peculiarly within his professional knowledge. When the court or jury can make its own deductions, deductions may not be made by witnesses. In this case the probable effects of an injury such as that suffered by the plaintiff could be shown only by the opinion of a competent physician. The physicians testified fully as to the facts on which they based their conclusions and were entitled to give their opinions on the probable effect of the injury that the plaintiff received. For the reasons stated, and others not here pertinent, judgment in favor of the plaintiff was affirmed.—*Pearce v. Rodell (Mich.), 276 N. W. 883.*

Society Proceedings

COMING MEETINGS

Academy of Physical Medicine, Washington, D. C., Oct. 24-26. Dr. Herman A. Osgood, 144 Commonwealth Ave., Boston, Secretary.

American Academy of Ophthalmology and Oto-Laryngology, Washington, D. C., Oct. 9-14. Dr. William P. Wherry, 107 South 17th St., Omaha, Executive Secretary.

American College of Surgeons, New York, Oct. 17-21. Dr. George W. Crile, 40 East Erie Street, Chicago, Chairman, Board of Regents.

American Public Health Association, Kansas City, Mo., Oct. 25-28. Dr. Reginald M. Atwater, 50 West 50th St., New York, Executive Secretary.

American Society of Tropical Medicine, Oklahoma City, Nov. 15-18. Dr. E. Harold Hinman, Wilson Dam, Ala., Secretary.

Associated Anesthetists of the United States and Canada, New York, Oct. 17-21. Dr. F. H. McMechan, 318 Hotel Westlake, Rocky River, Ohio, Secretary General.

Association of American Medical Colleges, Syracuse, N. Y., Oct. 24-26. Dr. Fred C. Zapffe, 5 South Wabash Ave., Chicago, Secretary.

Association of Military Surgeons of the United States, Rochester, Minn., Oct. 13-15. Dr. H. L. Gilchrist, Army Medical Museum, Washington, D. C., Secretary.

Central Association of Obstetricians and Gynecologists, Minneapolis, Oct. 6-8. Dr. William F. Mengert, University Hospitals, Iowa City, Secretary.

Central Society for Clinical Research, Chicago, Nov. 4-5. Dr. Lawrence D. Thompson, 4932 Maryland Ave., St. Louis, Secretary.

Clinical Orthopedic Society, Nashville, Tenn., and Birmingham, Ala., Oct. 7-8. Dr. H. Earle Conwell, 215 Medical Arts Bldg., Birmingham, Ala., Secretary.

Delaware, Medical Society of, Dover, Oct. 10-12. Dr. Allan V. Gilliland, Smyrna, Secretary.

Indiana State Medical Association, Indianapolis, Oct. 4-6. Mr. Thomas A. Hendricks, 23 East Ohio St., Indianapolis, Executive Secretary.

Inter-State Postgraduate Medical Association of North America, Philadelphia, Oct. 31-Nov. 4. Dr. W. B. Peck, 27 East Stephenson St., Freeport, Ill., Managing Director.

Kentucky State Medical Association, Louisville, Oct. 3-6. Dr. Arthur T. McCormack, 620 South Third St., Louisville, Secretary.

Omaha Mid-West Clinical Society, Omaha, Oct. 24-28. Dr. J. D. McCarthy, 107 South 17th St., Omaha, Secretary.

Pacific Association of Railway Surgeons, Los Angeles, Oct. 7-8. Dr. W. T. Cummins, Southern Pacific General Hospital, San Francisco, Secretary.

Pennsylvania, Medical Society of the State of, Scranton, Oct. 3-6. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh, Secretary.

Southern Medical Association, Oklahoma City, Nov. 15-18. Mr. C. P. Loranz, Empire Bldg., Birmingham, Ala., Secretary.

Southwestern Medical Association, El Paso, Texas, Nov. 3-5. Dr. Orville E. Egbert, 116 Mills St., El Paso, Texas, Secretary.

Vermont State Medical Society, Burlington, Oct. 6-7. Dr. B. F. Cook, 154 Bellevue Ave., Rutland, Secretary.

Virginia, Medical Society of, Danville, Oct. 4-6. Miss Agnes V. Edwards, 1200 East Clay St., Richmond, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1928 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but may be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Medical Sciences, Philadelphia

196: 153-304 (Aug.) 1938

United States Army's War in the Air Against the Mosquito-Borne Diseases. J. S. Simmons, Boston.—p. 153.

*Statistical Study of Acute Hemorrhagic Pancreatitis (Hemorrhagic Necrosis of Pancreas). H. A. Weiner and R. Tennant, New Haven, Conn.—p. 167.

Nature and Mechanism of Staining of Erythrocytic Reticulum. S. Nittis, Ann Arbor, Mich.—p. 177.

Acute Hemolytic Anemia. H. M. Greenwald, Brooklyn.—p. 179.

Observations on Etiology of Toxemias of Pregnancy: V. Etiologic Relationship Between Water Retention and Arterial Hypertension. M. B. Strauss, Boston.—p. 188.

Observations on Referred Pain of Cardiac Origin. S. Robertson and L. N. Katz, Chicago.—p. 199.

Paradoxic Embolism. D. W. Ingham, Rochester, Minn.—p. 201.

Radiologic Measurements of the Apicobasal Relaxation of the Lung During Artificial Pneumoperitoneum Treatment. A. L. Banyai, Wauwatosa, Wis.—p. 207.

Diabetic Coma Requiring an Unprecedented Amount of Insulin: Report of Case Manifesting Extreme Insulin Resistance. H. J. Wiener, New York.—p. 211.

Hyperinsulinism and Pregnancy: Report of Case. E. B. LeWinn, Philadelphia.—p. 217.

Uveoparotid Fever (Heerfordt's Syndrome): Neurologic Manifestations: Report of Two Cases. D. Arbuse and M. Madonick, New York.—p. 222.

Regeneration of Adrenal Gland Following Enucleation. D. J. Ingle and G. M. Higgins, Rochester, Minn.—p. 232.

Effects of Pressor Substance Obtained from Kidneys on the Renal Circulation of Rats and Dogs. A. Merrill, Atlanta, Ga.; R. H. Williams and T. R. Harrison, Nashville, Tenn.—p. 240.

Typhus Fever in Pennsylvania. H. F. Flippin, Philadelphia.—p. 246.

Disease and the Negro. G. Walsh and R. M. Pool, Fairfield, Ala.—p. 252.

Relationship of Orthopedic Surgery to Internal Medicine. H. T. Hyman, Long Branch, N. J.—p. 261.

*Effect of Prontosil and Related Compounds on Chemotropism of Leukocytes. D. R. Coman, Philadelphia.—p. 273.

Acute Hemorrhagic Pancreatitis.—The belief that alcohol is in some way related to acute hemorrhagic pancreatitis has developed in the department of pathology of the New Haven Hospital from a review of the clinical histories of fatal cases of this disease. This has been fortified by a not infrequent case with an explosive clinical course and striking postmortem observations, in the light of which Weiner and Tennant undertook an analysis of 4,000 necropsies. Each anatomic diagnosis was reviewed and all protocols in any way related to pancreatic disease were abstracted, with especial emphasis on the clinical history (including alcoholism), the chief anatomic causes of death and also the postmortem condition of the stomach, pancreas, liver and gallbladder. All the available slides of liver and pancreas in these cases were reviewed. There were thirty-eight instances of acute hemorrhagic pancreatitis and ninety-seven of chronic pancreatitis. In twenty-five of the acute cases, alcohol was an associated factor. In six, disease of the extrahepatic biliary tract was present. Of fifty-one persons dying during acute alcoholic episodes, twenty-seven had pancreatic lesions (twenty-five acute and two chronic). In forty-one instances of chronic alcoholism nineteen showed pancreatic lesions, all of a chronic nature. In fifty-one instances of periportal cirrhosis, twenty-five showed pancreatic lesions. In 343 cases of disease of the extrahepatic biliary tract there were six instances of acute pancreatitis and twenty-one of chronic pancreatitis. While the data offer no relation to the pathogenesis of acute pancreatitis, they indicate at least the complexity of the problem. The results show an increase of from forty to fifty times in the incidence of pancreatic disease when a history of alcoholism exists.

Sulfanilamide Compounds and Chemotropism of Leukocytes.—Coman conducted experiments using a sulfanilamide compound (Prontosil-Losung, Bayer) absorbed on kaolin, carbon and streptococci in an attempt to determine the chemotropic effect of the drug for polymorphonuclear leukocytes. Leukocytes were obtained from the peritoneal cavity of rabbits. Although the prontosil slightly reduced the negatively chemotropic effect of kaolin, it did not cause a positive chemotropic response. Adsorbed to carbon and to streptococci, the prontosil did not alter the directional movement of the leukocytes in relation to the adsorbing agents. There is, then, no evidence from these experiments that prontosil attracts leukocytes. Experiments in which sulfanilamide (Merck) was used as the attracting substance showed that this substance exerted a toxic effect on the leukocytes which was expressed in a cessation of their movements. Experiments in which a benzoyl derivative of sulfanilamide (setazine, Merck) was used as the source of attraction showed that this substance exerted only a weak attraction for the leukocytes and this was not constant. It seems unlikely from these experiments that the therapeutic action of these drugs is due to an increased chemotropism of polymorphonuclear leukocytes.

American Journal of Orthopsychiatry, Menasha, Wis.

8: 409-584 (July) 1938

Enuresis: A Method for Its Study and Treatment. O. H. Mowrer and Willie Mae Mowrer, New Haven, Conn.—p. 436.

Incidence of Enuresis and Age of Cessation in 100 Delinquents and 100 Sibling Controls. J. J. Michaels, Boston.—p. 460.

Clinical Experience with Play Therapy. M. Gitelson and collaborators, Chicago.—p. 466.

Active Play Therapy. J. C. Solomon, Baltimore.—p. 479.

Archives of Internal Medicine, Chicago

62: 181-354 (Aug.) 1938

*Culture of Human Marrow: Comparative Study of the Effects of Sulfanilamide and Antipneumococcus Serum on the Course of Experimental Pneumococcic Infections. E. E. Osgood, with technical assistance of Inez E. Brownlee, Portland, Ore.—p. 181.

Hyperparathyroidism Due to Idiopathic Hypertrophy (Hyperplasia?) of Parathyroid Tissue: Follow-Up Report of Six Cases. F. Albright, H. W. Sulkowitch and E. Bloomberg, Boston.—p. 199.

Removal of Intravenously Injected Bromsulphalein from the Blood Stream of the Dog: Comparison of the Removal of Intravenously Injected Bilirubin and That of Bromsulphalein. M. A. Mills and C. A. Dragstedt, Chicago.—p. 216.

Excretion of Bile Pigment and Hepatic Function in Diseases of the Blood. W. H. Barker, Baltimore.—p. 222.

*Experimental Streptococcic Endocarditis. R. A. Kinsella and R. O. Muether, St. Louis.—p. 247.

Lesions of Peripheral Nerves in Thrombo-Angiitis Obliterans: Clinicopathologic Study. N. W. Barker, Rochester, Minn.—p. 271.

Boeck's Sarcoid: Report of Case, with Clinical Diagnosis Confirmed at Autopsy. J. Spencer and S. Warren, Boston.—p. 285.

*Oral Ragweed Pollen Therapy: Clinical Results of Experiments on Gastrointestinal Absorption. T. B. Bernstein and S. M. Feinberg, Chicago.—p. 297.

Infectious Diseases: Review of Current Literature. H. A. Reimann, Philadelphia.—p. 305.

Culture of Human Marrow.—Osgood found by studying cultures of human marrow that sulfanilamide exhibits a slight bacteriostatic action on pneumococcic infections which is increased by an increase in concentration. Even 0.3 unit per cubic centimeter of specific antipneumococcus serum is more effective against the type I pneumococcus than is sulfanilamide alone. Sulfanilamide plus any given dose of antiserum less than the amount which will by itself reduce colony counts to nearly zero is more effective than corresponding doses of antiserum alone. The results support the view that sulfanilamide renders the organism more vulnerable to bactericidal substances present in the serum. If the results of these in vitro experiments are applicable to infections in human beings, sulfanilamide therapy should be of value in pneumococcic pneumonia and might delay death in pneumococcic meningitis, but alone it will not prove as effective as even small amounts of type-specific antiserum. If used in conjunction with antiserum it should further lower the mortality with the present doses of antiserum or should give an equally low mortality with smaller doses of antiserum.

Experimental Streptococcic Endocarditis.—Kinsella and Muether injured the mitral valve or the chordae tendineae of seventeen dogs and then fed them living cultures of non-

hemolytic streptococci either mixed with food or by stomach tube. Ten of the animals became sick, displayed positive results of blood culture and died. At necropsy these infected animals had bacterial endocarditis. The bacteria in the vegetations were found to be identical with those that had been fed to the animals. Bacteria entering the animal body through the mouth may become implanted on an injured area within the body. The exact route which these bacteria follow is not determined.

Oral Ragweed Pollen Therapy.—Bernstein and Feinberg gave extract of ragweed pollen to twenty patients allergic to ragweed. The duration of treatment was from one to three weeks. In determining the strength of the initial doses the relation of the oral to the hypodermic dose was kept in mind. One drop of a 1:33 extract of ragweed pollen was regarded as a probably safe initial dose, since it is about 450 times the strength of the first dose (0.05 cc. of a 1:10,000 extract) usually given hypodermically. The doses were given three times daily well diluted. In most instances the maximal dose was from 10 to 15 drops at the end of a week. In two cases a maximal dose of 30 drops was used. No benefit whatever was experienced by eighteen patients with regard to the symptoms of hay fever and asthma. Two obtained moderate improvement, in one of whom while there was some improvement in the hay fever there was no improvement in the asthma. In other words, there was no amelioration of the asthma in any instance. In six patients the pollen extract caused gastrointestinal disturbances, consisting mainly of colicky addominal pain and nausea.

Archives of Neurology and Psychiatry, Chicago

40: 227-416 (Aug.) 1938

*Biopsy Studies of Cerebral Pathologic Changes in Schizophrenia and Manic-Depressive Psychosis. A. R. Elvidge and G. E. Reed, Montreal.—p. 227.
Sweat Secretion in Man: III. Clinical Observations on Sweating Produced by Pilocarpine and Mecholyl. C. F. List and M. M. Peet, Ann Arbor, Mich.—p. 269.
Intracerebral Blood Flow: Experimental Study. N. C. Norcross, Philadelphia.—p. 291.
*Mechanism of After-Contraction: Further Studies. M. R. Sapirstein, R. C. Herman and I. S. Wechsler, New York.—p. 300.
Intercellular Substance of the Cerebral Cortex (Nissl's Cerebral Gray Matter): Physiologic Significance. A. E. Taft, Philadelphia.—p. 313.
Moro Reflex and Startle Pattern. K. Goldstein, C. Landis, W. A. Hunt and F. M. Clarke, New York.—p. 322.
Arnold-Chiari Malformation and Its Operative Treatment. W. Penfield and D. F. Coburn, Montreal.—p. 328.
Distribution of Affected Nerve Cells in a Case of Amyotonia Congenita. J. L. Conel, Boston.—p. 337.
Thalamic Dysfunction: Report of Case in Which a Thalamic Syndrome Was Treated by Excision of a Porencephalic Cyst. H. L. Kozol, Boston.—p. 352.

Cerebral Changes in Psychosis.—Elvidge and Reed obtained twenty-six specimens of cerebral tissue for biopsy from nineteen psychotic patients between 20 and 40 years of age; thirteen with schizophrenia, five with manic-depressive psychosis and one with so-called toxic encephalitis. A second operation was performed on seven of the patients at the end of from one to two years, and thus useful data were furnished as a control. Sixteen specimens serving as controls were taken from routine surgical material with a similar or an identical technic. Swelling of the oligodendroglia cells occurred in association with schizophrenia and manic-depressive psychosis. There was often accompanying mild hypertrophy of the astrocytes. Two main types of oligodendroglial change were observed: that in which the nuclei were normal and that in which they were pyknotic. Swelling of oligodendroglia cells was observed in two patients with status epilepticus who were mentally confused between seizures. It existed in one patient at the time of an epileptic seizure. The change in the oligodendroglia cells in psychotic patients occurred in the white matter. It may be general or patchy in distribution. At a depth of 1 cm. and in the deeper layers it was often more intense. In view of the changes in the oligodendroglia cells, it is suggested that the mental phenomena are associated with massive physiologic disturbances in associational and commissural fibrous pathways in the brain. In this way impulses from different parts of the brain are interrupted, with consequent disturbance and loss of control in the intellectual, volitional and emotional fields. By analogy with the other states in which swelling of oligodendroglia cells is observed, it is justifiable to assume that in psychotic states also there may be a causal toxic or metabolic factor.

After-Contraction.—How far one may utilize the concept of after-contraction in studies of ordinary motor learning Sapirstein and his collaborators do not say, but for the production of after-contraction a large initial stimulus produced by external forces is not necessary. Supporting the weight of the limb itself is sufficient. In walking or running there is a repetitive movement, perfectly coordinated, which eventually is made with almost no conscious effort; indeed, the movement seems entirely automatic. It is easily believable that a basic factor involved here is that represented by after-contraction, which is a sustained cortical excitatory state responding in a rhythmic fashion to stimuli of which the subject is unconscious. Physiologically, after-contraction is influenced by facilitation, fatigue and changes in initial load and duration of effort. The phenomenon is always reenforced by simultaneous contraction of ipsilateral muscles and is frequently inhibited by contraction of contralateral muscles. A relatively normal reaction is associated with tabes and cerebellar syndromes, a prolonged after-contraction with paralysis agitans and a diminished response with disease of the pyramidal tracts. After-contraction is mainly an after-discharge from the cortex or its projection pathways. It is modified by other parts of the nervous system, as is voluntary activity. Suggestions are offered concerning the usefulness of after-contraction as a method of investigating the physiologic behavior of the cortex and of studying drugs used in controlling its excitability. Theoretical views are advanced as to the possible role of after-contraction in habit formation.

Archives of Ophthalmology, Chicago

20: 175-358 (Aug.) 1938

Disturbances of Vertical Motor Muscles of the Eyes. A. Bielschowsky, Hanover, N. H.—p. 175.
Perimetric Studies in Syphilitic Optic Neuropathies. Louise L. Sloan and A. C. Woods, Baltimore.—p. 201.
Cancer of the Eyelids, Conjunctiva and Cornea: II. Squamous Cell Epithelioma. H. L. Birge, Rochester, Minn.—p. 254.
*Treatment of Staphylococcic Conjunctivitis with Staphylococcus Toxoid: Preliminary Note. P. Thygeson, New York.—p. 271.
Mannitol Fermentation as Indicator of Conjunctival Pathogenicity of Staphylococci. P. Thygeson, New York.—p. 274.
Recurrent Retinal and Vitreous Hemorrhages in the Young—Eales' Disease: Report of Two Cases. R. T. Paton, New York.—p. 276.
An Ophthalmic Carriage. J. N. Evans, Brooklyn.—p. 286.
Topography and Frequency of Complications of Uveal Sarcoma. B. Kronenberg, New York.—p. 290.
Inositol in Ocular Tissues. A. C. Krause and R. Weekers, Chicago.—p. 299.
Detachment of the Retina: Summary of Modern Opinions. T. D. Allen, Chicago.—p. 307.

Staphylococcic Conjunctivitis.—In view of the efficacy of immunization with staphylococcus toxin in protecting rabbits against instillations of toxin which would produce severe conjunctivitis in normal rabbits, Thygeson attempted to obtain healing in fifty-seven human beings with conjunctivitis by immunization with toxoid. Only persons were chosen whose conjunctivitis had resisted local treatment for not less than two months. The majority of the patients had had conjunctivitis for more than a year. The toxoid was given biweekly, starting with an initial injection of 0.01 cc. of dilution. 2. The dose was increased to a maximum of 1 cc. in steps of 0.02, 0.04, 0.06, 0.08, 0.1, 0.2, 0.4, 0.6 and 0.8 cc. Injections of less than 0.5 cc. were given intradermally and the remainder were given subcutaneously. In cases in which noticeable improvement did not occur on completion of the series, injections of 0.5 cc. were continued at weekly intervals for at least six weeks. Healing occurred in twenty-one of the fifty-seven patients, nineteen showed clinical improvement and the condition of seventeen remained unchanged. The cultures of twenty-four of the fifty-seven patients became negative. There was a recurrence of symptoms after periods varying from four to six months in eight of the persons in whom clinical healing occurred. In all these the symptoms disappeared after a second course of toxoid therapy. This recurrence was probably related to the fact that in seven of the eight patients

some toxigenic staphylococci were still present after healing. The cultures of the thirteen patients in whom healing occurred, and who have as yet had no recurrence, were negative after healing. The results obtained warrant further clinical trial of staphylococcus toxoid.

Florida Medical Association Journal, Jacksonville

25: 53-104 (Aug.) 1938

Ectopic Pregnancy. L. J. Netto, West Palm Beach.—p. 65.
Therapy in Modern Psychiatry. W. G. Miles, Chattahoochee.—p. 71.
Gonococcic Peritonitis of the Upper Right Quadrant. T. F. Hahn, De Land.—p. 73.
Cooperation of Railroad Surgeons. W. J. Lancaster, Wilmington, N. C. —p. 75.
Relief of Pain by Intraspinal (Subarachnoid) Injection of Alcohol. C. S. Franckle, St. Petersburg.—p. 80.

Iowa State Medical Society Journal, Des Moines

28: 373-420 (Aug.) 1938

Diseases Associated with Characteristic Changes in the Red Blood Cells: Microcytic and Macrocytic Anemias. C. C. Sturgis, Ann Arbor, Mich. —p. 373.
Regional Enteritis. J. V. Prouty, Cedar Rapids.—p. 379.
Management of Uterine Malignancy. R. F. Martin, Sioux City.—p. 382.
Prevention of Poliomyelitis. F. Moore, Des Moines.—p. 385.
*Delayed Resolution in Bronchopneumonia. F. N. Cole, Iowa Falls.—p. 389.
Manifestations of Insulin Hypoglycemia Mistaken for Other Disease in Patients with Known Diabetes Mellitus. W. L. Randall, Hampton, A. E. Feller and J. A. Greene, Iowa City.—p. 392.

Delayed Resolution in Bronchopneumonia.—In considering the problem of delayed resolution in bronchopneumonia it seems likely to Cole that one is not dealing with a true pathologic entity but with a variety of conditions. There is a definite need for more clinical investigation under controlled conditions. Many cases of this nature are seen in the home in which facilities for careful diagnostic studies are lacking. Under ideal conditions, one should have serial roentgenograms in every case of bronchopneumonia. Bronchoscopic examination should be made of those patients who fail to recover promptly. It may be found that so-called nonresolution is really due to localized areas of atelectasis or to occlusion of a bronchus or a bronchiole. Treatment is bound to be empiric until the condition is better understood.

Journal of Thoracic Surgery, St. Louis

7: 575-690 (Aug.) 1938

Extrapleural Pneumothorax. R. Belsey, London, England.—p. 575.
*Extrapleural Pneumothorax in Treatment of Pulmonary Tuberculosis: Preliminary Report. R. H. Overholt, Boston, and O. S. Tubbs, London, England.—p. 591.
Resection of Thoracic Esophagus: Clinical and Experimental Study. W. E. Adams, L. Escudero, H. G. Aronsohn and M. M. Shaw, Chicago.—p. 605.
Carcinoma of Lower Thoracic Esophagus: Report of Successful Resection and Esophagogastrostomy. W. E. Adams and D. B. Phemister, Chicago.—p. 621.
Upper Esophagostomy: Its Indications and Uses. C. Eggers, New York. —p. 633.
Role of Dual Pulmonary Circulation in Various Pathologic Conditions of the Lungs. D. A. Wood and Miriam Miller, San Francisco.—p. 649.
Observations on Sources of Pulmonary Hemorrhage and Attempts at Its Control. L. Eloesser, San Francisco.—p. 671.

Extrapleural Pneumothorax in Pulmonary Tuberculosis.—Up to the present Overholt and Tubbs selected only those patients for extrapleural pneumothorax for whom any other form of collapse therapy offered no hope of a successful outcome. Extrapleural pneumothorax is not introduced to replace the modern selective thoracoplasty but is an alternative measure when the latter is contraindicated. The factors which render the patient with pulmonary tuberculosis unsuitable for thoracoplasty are evidence of too great activity, extensive bilateral lesions of a fibrocavernous nature and complicating factors (insufficient cardiovascular reserve, generalized emphysema, asthma and the like). The operation has been performed thirty-one times (in twenty-eight patients) under cyclopropane and oxygen inhalation anesthesia or a combination of local infiltration with paravertebral block of the upper intercosal nerves, 1 per cent procaine hydrochloride being used. On return to the ward, an oxygen tent has rarely been needed even in the bad risk patients. Intravenous infusion has been used if the blood pressure fell below 100 systolic, so that the patient may sit up soon after operation. All the patients had more or less interstitial emphysema during the first twenty-four hours, but in no case has it caused any distress other than slight tenderness of the affected tissues. Sputum was not retained for more than thirty-six hours. Following pneumonolysis, patients are able to expectorate more efficiently and sooner than after thoracoplasty. The frequency and amount of air refills to maintain the space so as to give the desired selective collapse have been controlled by frequent roentgenograms, fluoroscopy and consideration of the manometric pressures. In three cases almost the whole space became filled with blood clots which could not be aspirated through a needle. Infection in the extrapleural space developed in four patients. In three of these there is definite evidence of a bronchial fistula. In another case evidence is lacking, although it is possible that the lateral wall of the cavity became necrotic because of its separation from the wall of the chest. Regardless of this complication, the patient has improved sufficiently to consider thoracoplasty. The authors believe that most of the patients will eventually require conversion of the extrapleural pneumothorax to the permanent collapse of thoracoplasty. This prediction is made because of the extensive disease present in those selected for this form of treatment. Should the operation eventually be applied more widely to include young patients with less extensive disease, the ultimate fate of the space would be subject to the same rules that apply to an intrapleural pneumothorax.

Kentucky Medical Journal, Bowling Green

36: 301-348 (Aug.) 1938

Practical Diagnosis and Treatment of the Acute Abdomen. L. R. Ellars, Louisville.—p. 303.
Common Errors in the Diagnosis of Hyperthyroidism. A. E. Grimes, Lexington.—p. 307.
The Physiology of Edema Formation. H. Lawson, Louisville.—p. 309.
Disease Masquerades in Heart Symptoms. E. F. Horine, Louisville.—p. 313.
Intussusception in Infancy and Childhood. G. P. Grigsby and S. E. Kaplan, Louisville.—p. 318.
Agranulocytosis. J. Stites and F. M. Stites, Louisville.—p. 324.
Anesthesia. D. M. Dollar, Louisville.—p. 328.
Study of Maternal Deaths, Infant Deaths and Cesarean Sections in the Louisville Kentucky Hospitals. W. T. McConnell, Louisville.—p. 336.
Postural Treatment of Pulmonary Tuberculosis. B. L. Brock and T. A. Woodson, Louisville.—p. 343.

Maine Medical Journal, Portland

29: 161-180 (Aug.) 1938

Low Transverse Cervical Cesarean Section. A. P. Leighton, Portland. —p. 161.
Mortality in Surgical Diabetes in the General Hospital: Medical Study of 100 Operated Cases. E. R. Blaisdell, Portland.—p. 165.
Infectious Mononucleosis (Glandular Fever): Report of Case Presenting Symptoms of Acute Appendicitis. R. A. Beliveau and B. W. Russell, Lewiston.—p. 167.

Missouri State Medical Assn. Journal, St. Louis

35: 299-342 (Aug.) 1938

Menstruation and Dysmenorrhea. W. B. Brown, Columbia.—p. 299.
Present Day Therapy of Varicose Veins. C. K. Higgins, St. Louis.—p. 305.
Intussusception with Procidentia Through an Ulcerated Ventral Hernia: Report of Case. H. F. Burkwall, Kansas City.—p. 308.
Early Symptoms of Genito-Urinary Disease. H. M. Young, Columbia. —p. 310.
Roentgenologist Looks at Gastric Cancer. S. A. Levey, St. Louis.—p. 316.
Practical Method of Blood Transfusion in the Home. J. H. Keim, Kennett.—p. 320.
The Future of Thyroid Surgery. W. Bartlett, St. Louis.—p. 322.

Nebraska State Medical Journal, Lincoln

23: 281-320 (Aug.) 1938

Immunologic Aspects of Syphilis. C. C. Dennie, Kansas City, Kan.—p. 281.
Nebraska's Program of Venereal Disease Control. E. G. Zimmerer, Lincoln.—p. 286.
Treatment of Acute and Subacute Gonorrhea. W. J. McMartin, Omaha. —p. 289.
Early Syphilis and Its Cutaneous Manifestations. C. C. Tomlinson, Omaha.—p. 292.
Prevention and Treatment of Neurosyphilis: Results in Seventy-Two Cases of Asymptomatic and Clinical Neurosyphilis by Combined Artificial Fever and Chemotherapy. A. E. Bennett and M. D. Lewis, Omaha.—p. 295.
Cardiovascular Disease. J. C. Thompson, Lincoln.—p. 301.
Fever Therapy in Treatment of Gonorrhea. C. A. Owens, Omaha.—p. 308.

Northwest Medicine, Seattle

37: 231-270 (Aug.) 1938

Chronic Cicatricial Obstruction of Extrahepatic Bile Ducts. C. E. Hagyard, Seattle.—p. 237.
Primary Pyocyaneous Meningitis: Report of Case Ending in Recovery. E. H. Berger, Portland, Ore.—p. 242.
Residual Abscesses After Ruptured Appendicitis. M. S. Rosenblatt, Portland, Ore.—p. 245.
Modern Rationale in the Treatment of Pneumonia. H. J. Friedman, Seattle.—p. 246.
Improved Method of Administering Oxygen by Nasal Catheter. T. W. Houk, Seattle.—p. 248.
Public Health Aspects of Pneumonia. D. G. Evans, Seattle.—p. 250.
Inexpensive Watch Glass Museum Mountings: Improved Technic. C. P. Larson, Fort Steilacoom, Wash., and E. J. Levin, Tacoma, Wash.—p. 254.

Ohio State Medical Journal, Columbus

34: 841-960 (Aug.) 1938

Bilateral Nephrolithiasis and Ureterolithiasis. I. Abell, Louisville, Ky.—p. 857.
Self Selection of Diet Experiment: Its Significance for Feeding in the Home. Clara M. Davis, Winnetka, Ill.—p. 862.
Spontaneous Hypoglycemia Associated with Pancreatic Adenoma: Case Report with Operation and Autopsy. L. A. Levison and T. L. Ramsey, Toledo.—p. 869.
Management of Burns of the Cornea. A. M. Culler, Dayton.—p. 873.
Hypophysial Cachexia (Simmonds' Disease): Report of Two Cases with Autopsy Findings. M. A. Davis, Painesville, and Beatrice Bostle, Columbus.—p. 879.
Acute Intestinal Obstruction. B. H. Nichols, Cleveland.—p. 884.
Place of the Hospital in Maternal Welfare. P. F. Williams, Philadelphia.—p. 887.
Poliomyelitis: Symptomatology and Treatment: Part II. F. E. Stevenson, Cincinnati.—p. 893.
Production of Collateral Circulation and Relief of Vasospasm in Peripheral Vascular Disease. L. N. Atlas, Cleveland.—p. 899.
Classification of Tumors. L. A. Pomeroy, Cleveland.—p. 903.

Pennsylvania Medical Journal, Harrisburg

41: 969-1082 (Aug.) 1938

Aneurysms: Statistical Study of Eighty-Four Cases from Surgical Department of Philadelphia General Hospital. E. R. Saleeby and P. A. McCarthy, Philadelphia.—p. 969.
Some Observations Concerning Chronic Maxillary Sinusitis. H. D. Rentschler, Sayre.—p. 975.
Treatment of Infected Abrasions of the Cornea. C. F. Kutscher, Pittsburgh.—p. 979.
Hypothyroidism: Etiologic Factor in Eclampsia. W. B. Patterson, R. E. Nicodemus and H. F. Hunt, Danville.—p. 983.
Plea for Conservatism in Appendectomy for Chronic Appendicitis: Observations on the Spastic, Irritable or Unstable Colon Syndrome. W. A. Swalm and L. M. Morrison, Philadelphia.—p. 988.
Roentgenologic Diagnosis of Various Juxtadiaphragmatic Lesions, Particularly Perinephric Abscess. R. D. Bacon, Erie.—p. 992.
Congenital Cataract. B. Chance, Philadelphia.—p. 1001.
Value of Blood Studies in the Treatment of Lupus Erythematosus. J. J. Hecht and S. R. Perrin, Pittsburgh.—p. 1006.
Endocrine Factors in Human Sterility: Evaluation of Diagnostic and Therapeutic Measures. C. Mazer, S. L. Israel and C. W. Charny, Philadelphia.—p. 1009.
*Persistence of Pain Following Multiple Operations for Cure of Sinus Disease. S. R. Skillern Jr., Philadelphia.—p. 1017.
Tumors of the Larynx, Benign and Malignant: Diagnosis, Prognosis, and Treatment. G. Tucker, Philadelphia.—p. 1023.
Attempt to Evaluate Dyspnea by Circulation Studies in Chronic Heart and Lung Disease. E. Weiss and M. Kleinbart, Philadelphia.—p. 1026.

Pain Following Operations for Sinus Disease.—Skillern presents the variable theories on the persistence of sinus pain after operations on the sinus as expressed by sixteen leading rhinologists. A tabulation of the opinions gives the following causes in order of frequency for the persistence of pain: incomplete operation, disease elsewhere than in the sinus operated on, systemic disease causing symptoms of sinusitis, synechiae or scar tissue blocking drainage or enmeshing the nerve, direct injury to or interference with a nerve, operation on the ethmoids and turbinates for insufficient reason, individual nervous reaction to pain, neuritis of the fifth cranial nerve, atypical neuralgia of unknown origin, reaction to insult of the periosteum and bone, injury to the sympathetic plexus and diversion of normal air currents within the nose. As long as there is any evidence of sinus infection the obligations of the otolaryngologist have not been fulfilled, and the persistence of apparent sinus pain means further study in conjunction with specialists in other fields of medicine until they have found the cause and, if possible, relief has been obtained. The author believes that the persistence of pain (1) in the frontal sinus after radical operation may be due to failure to remove every vestige of infected material, localized meningitis or osteomyelitis, abscess in the frontal lobe and/or infection in another sinus; (2) in the maxillary sinus to injury to the infra-orbital foramen, injury to the dental or infra-orbital nerve, reinfection from overlying sinuses, failure to remove all the infective material from the sinus and infection of an adjacent cell (anterior ethmoid) causing symptoms resembling those of maxillary sinusitis, and (3) in the ethmoid capsule and sphenoid sinus traumatized periosteum or bone near the foramen, direct injury to the nerves or blood vessels, proximity of the meninges (localized meningitis or osteomyelitis) and failure to open the long, narrow, fronto-ethmoid cell, the thin slitlike orbital or any anatomically misplaced ethmoid cell that may be infected. The ethmoid capsule and the sphenoid are considered as one, as synechiae may follow an operation, with the walling off of isolated areas of infection.

Public Health Reports, Washington, D. C.

53: 1337-1380 (Aug. 5) 1938

Human Infection with Bacillus Pseudotuberculosis Rodentium: Case. N. H. Topping, C. E. Watts and R. D. Lillie.—p. 1340.
Studies on Dental Caries: V. Familial Resemblance in the Caries Experience of Siblings. H. Klein and C. E. Palmer.—p. 1353.
Unsuccessful Treatment of Malaria with Sulfonamide Compounds. G. H. Faget, M. R. Palmer and R. O. Sherwood.—p. 1364.

53: 1381-1442 (Aug. 12) 1938

Comparison of Precipitation Reaction in Immune Serum Agar Plates with Protection of Mice by Antimeningococcus Serum. Margaret Pittman, Sara E. Branham and Elsie M. Sockrider.—p. 1400.

Rhode Island Medical Journal, Providence

21: 113-126 (Aug.) 1938

Surgical Aspects of Peptic Ulcer. R. Zollinger, Boston.—p. 113.
Recent Advances in the Pathology of Diabetes Mellitus. S. Warren, Boston.—p. 117.
Clinical Aspects of Testicular Tumors. W. C. Quinby, Boston.—p. 119.

Surgery, St. Louis

4: 161-320 (Aug.) 1938

Delayed Operation in Treatment of Perforated Appendix. C. E. Gardner Jr., Durham, N. C.—p. 161.
End Results Following Removal of "Inactive" Appendix. C. E. Rea and L. Kleinsasser, Minneapolis.—p. 179.
*Tuberculous Peritonitis: Speculation on Cause of Improvement Following Surgery. M. J. Brown, Sayre, Pa.—p. 185.
Chronic Subdural Hematoma: Diagnosis and Treatment. R. G. Coblentz, Baltimore.—p. 194.
Subdural Hematoma, Acute and Chronic, with Some Remarks About Treatment. A. Kaplan, New York.—p. 211.
Effect on Blood Flow of Decreasing the Lumen of a Blood Vessel. F. C. Mann, and by invitation J. F. Herrick, H. E. Essex and E. J. Baldes, Rochester, Minn.—p. 249.
Report of 500 Blood Transfusions. E. H. Fell, Chicago.—p. 253.
Blood Transfusion and Storage of Blood for Emergency Procedures. E. B. Tuohy, Rochester, Minn.—p. 261.

Tuberculous Peritonitis.—Since the favorable results of operation in tuberculous peritonitis are out of proportion to the amount of surgical work performed, there must be some other explanation of why these patients improve. It seems likely to Brown that in some cases equivalent improvement may be accomplished by the use of closed ether anesthesia alone. A temporary anoxemia produced by the anesthesia might be an explanation for the apparent cures. The tubercle bacilli are known to be aerobic organisms. From the known facts of culturing the tubercle bacilli, the reduced oxygen intake of the body would explain, at least partially, the improvement that follows when ether anesthesia alone is administered. The chemical study of the tubercle bacillus shows that such compounds as lipoids, fatty acids, acetone-soluble fat and wax can be isolated. Since the blood carries a large volume of ether vapor during anesthesia, it is possible that some chemical reaction may take place with one or more of these substances to cause permanent injury to the organisms or to produce an oxygen impermeable membrane about them. Such speculations on a chemical basis would tend to uphold further the proposed theory of anoxemia as an explanation of improvement in cases of tuberculous peritonitis following closed ether anesthesia alone or accompanying a surgical procedure. A study of cases of tuberculous peritonitis in which operation has been performed with spinal anesthesia would do much to settle the question of whether inhalation anesthesia is a factor in the improvement.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Ophthalmology, London

22: 449-512 (Aug.) 1938

Rhinosporidiosis on the Eye: Case. H. Kaye.—p. 449.
Ablatio Falciformis Congenita (Retinal Fold). H. Weve.—p. 456.
Some Clinical Notes on Nature of Retinal Venous Pulse. N. Pines. —p. 470.
Lightreserve for Occupations in Sight-Saving Classes. R. A. Kaz.—p. 482.
Children with Defective Vision, in Need or Not of Sight-Saving Classes. R. A. Kaz.—p. 486.

East African Medical Journal, Nairobi

15: 95-128 (July) 1938

Cutaneous Manifestations of Vitamin Deficiency. J. H. Sequeira.—p. 96.
Air Raid Precautions. J. R. Gregory.—p. 115.

Journal of Physiology, London

93: 75-171 (July 14) 1938

The Carotid Sinus and Blood Regeneration. A. L. Latner.—p. 75.
Osmotic Pressure of Fetal and Maternal Serums in Sheep. E. F. McCarthy.—p. 81.
Transmission of Impulses by Ganglionic Direct Fibers. D. P. C. Lloyd. —p. 86.
Effect of Asphyxia on the Heart Rate of Rabbits at Different Ages. D. J. Bauer.—p. 90.
Segmental Distribution of Certain Visceral Afferent Neurons of the Pupillodilator Reflex in the Cat. B. A. McSwiney and S. F. Suffolk. —p. 104.
Carbonic Anhydrase Activity Inside Corpuscles. Enzyme-Substrate Accessibility Factors. V. H. Booth.—p. 117.
Action of Adrenalin, Acetylcholine and Other Substances on Nerve-Free Vessels (Human Placenta). U. S. v. Euler.—p. 129.
*Effects of Prolonged Muscular Exercise on Metabolism. J. N. Mills.—p. 144.
Action of Adrenalin in Accelerating Removal of Blood Sugar by Peripheral Tissues. H. P. Himsworth and D. B. M. Scott.—p. 159.

Exercise and Metabolism.—Mills studied the metabolism of two subjects who were not in athletic training before and after a walk of ten miles in the postabsorptive state. One subject, the author, who lived habitually on a high carbohydrate diet, showed an inconstant lowering of the respiratory quotient after the walk, but no ketonuria or depression of tolerance to dextrose, even when he restricted the carbohydrate in his diet. The other subject, who habitually consumed a lower proportion of carbohydrate, always showed a low respiratory quotient and ketosis after a walk unless he greatly increased the intake of carbohydrate in his diet. His tolerance to dextrose was considerably depressed after the walk, but if he had been living on a high carbohydrate diet this depression was absent. Curves of blood sugar have been plotted for the second subject after intravenous injection of insulin. Those after exercise did not differ from those before in the phase of falling blood sugar, showing that the depressed tolerance to dextrose was not due to a reduced sensitivity to insulin. After exercise there was, however, a delay in the return of the blood sugar to normal and determinations of respiratory exchange after injection of insulin suggested that at this time this may have been due to a higher level of carbohydrate metabolism. Insulin was found to raise the respiratory quotient much further after exercise than before.

Lancet, London

2: 235-294 (July 30) 1938

The Approach to Gastric Surgery. W. H. Ogilvie.—p. 235.
Pneumonitis. J. Maxwell.—p. 239.
*Precision in Spinal Anesthesia. N. C. Lake.—p. 241.
*Hemolytic Streptococcus in the Etiology of Rheumatic Fever and Rheumatoid Arthritis. W. Goldie.—p. 246.
*Correction of the Sedimentation Rate for Anemia. M. Hynes and L. E. H. Whitby.—p. 249.

Precision in Spinal Anesthesia.—Lake outlines a technic for precise spinal anesthesia in the carrying out of which the patient, who may have had a preliminary injection of morphine and atropine, is given an injection of 1 grain (0.065 Gm.) of ephedrine and is then placed face downward on the operating table. Pillows are now packed under the lower part of the chest to produce a well marked dorsal curve. The back is marked with iodine to indicate the intercristal plane, the second and third lumbar interval and the seventh dorsal spinous process. The dorsal curve is now "sighted" against a horizontal black line painted on the wall of the operating room, and the table is tilted until the marked seventh spinous process lies at the apex of the curve. The head is kept flexed well down so that no solution can reach the cervical region. By means of the same solution with a hypodermic needle a wheal is raised on the skin at the point of injection and a little of the solution is also placed along the proposed needle track. A fine-bore stainless steel needle is now introduced at this level in a direction exactly vertical to the surface in all planes. The passage of the needle should be deliberate and slow so that the penetration of the dura can be easily felt. The needle is rotated and pushed on slightly to determine that the aperture is well within the dura and it is then turned so that the lateral aperture points up the spine. A syringe is attached to the needle, care being taken that the latter suffers no displacement. The solution, 1:1,500 nupercaine in saline solution, warmed to body temperature, is injected slowly to avoid turbulence and, as far as possible, to get the nupercaine solution to travel as a "bundle" to the highest point of the theca. At least two or three minutes should be taken to introduce from 6 to 9 cc. of the solution. The quantity to be injected varies a little with the size of the patient and the nature and expected duration of the operation. When the injection is completed the needle and syringe are held steady for a further thirty seconds and then withdrawn. The patient now remains in the same posture without movement for ten minutes and is then turned on his back, the pillows being removed and the table tilted into the head-down position. The operation may be immediately started. The author has now used this technic for nearly three years in many hundreds of cases and has obtained uniformly good results. It requires no complicated apparatus beyond the ordinary tilting operating table. Severe headaches are rare and there have been no other neurologic sequelae.

Hemolytic Streptococcus and Rheumatism.—Goldie states that there is clinical, immunologic and pathologic evidence of an etiologic relationship between rheumatic fever and rheumatoid arthritis. Immunologic data are presented to show that infection with the hemolytic streptococcus is more prevalent in these two diseases than in normal persons. Myocardial changes showing some resemblance to those characteristic of rheumatic fever have been produced in animals sensitized to bacterial protein, and this lends support to the theory that rheumatic fever and rheumatoid arthritis result from sensitization to the hemolytic streptococcus.

Sedimentation Rate and Anemia.—Hynes and Whitby constructed "sedimentation curves" according to the method of Wintrobe and Landsberg (1935). From observations of thirty-eight normal students a normal curve was constructed and the limits of the normal sedimentation rate were confirmed. Curves were made from forty-six cases with abnormal sedimentation rates. Curves were also made from eleven anemic patients whose blood, when reconstructed and rendered nonanemic by the addition of corpuscles, had normal sedimentation rates. These curves, whatever the degree of anemia, were precisely of the type obtained from normal students with similar sedimentation rates. In the same way the degree of anemia was found not to influence the shape of the curves for cases with abnormal sedimentation rates of the same order. These facts confirm the principle of correcting the sedimentation rate for anemia in terms of the hematocrit reading according to the method of Wintrobe and Landsberg.

Medical Journal of Australia, Sydney

2: 71-108 (July 16) 1938

Early Diagnosis of Cancer of Cervix. H. H. Schlink and C. L. Chapman.—p. 71.
Treatment of Cancer of Cervix Uteri. H. H. Schlink and C. L. Chapman.—p. 74.
Casualty Surgery. A. Aspinall.—p. 81.
Manipulative Surgery. W. K. Hughes.—p. 83.
The Contact Lens. J. D. Maude.—p. 85.
X-Ray Therapy in Sinusitis. H. Mitchell.—p. 86.
Blood Uric Acid Estimation in Eclampsia. T. Rose.—p. 87.
Fractures of the Spine, with Special Reference to Laminectomy. N. Little.—p. 89.
Analysis of Autopsy Findings in 200 Cases of Pulmonary Tuberculosis. A. H. Penington.—p. 90.

Journal Belge de Neurol. et de Psychiat., Brussels

38: 495-558 (July) 1938. Partial Index

Nontraumatic Intracerebral Hematoma: Operation and Cure. L. Laruelle and L. Massion-Verniory.—p. 495.
Pathogenesis of Vestibular Disturbances in Lesions of Spinal Cord. J. Helsmoortel Jr.—p. 504.
*Prospects of Survival and Cure in Dementia Paralytica: Eighty Catamneses Ten Years After Malariotherapy. P. Vervaeck.—p. 508.
Vertebral Anomalies and Radicular Disturbances. M. Leroy.—p. 520.
Value of Metrazol Test in Diagnosis of Epilepsy. G. Muyle.—p. 525.

Survival and Cure in Dementia Paralytica.—Vervaeck points out that the majority of about 2,000 publications that have appeared since the beginning of the era of malaria therapy of dementia paralytica is concerned with the clinical and social results of this treatment. Reviewing the figures given by different investigators about the percentages of remissions obtained with this treatment, the author found that they differ widely. He investigated the condition of patients with dementia paralytica ten years after they had been treated at a psychiatric clinic in Brussels. Investigations were made on the men who had been treated during the years 1926 and 1927. Dementia paralytica being less frequent in women, the follow-up studies were extended to the female patients who received treatment during the four years from 1925 to 1928 inclusive. Of fifty male patients, forty-one had been subjected to malaria therapy; and of fifty-three women, forty-two had been so treated. Of the forty-one male patients who had been treated with malaria, seven were still outside an asylum ten years after, but one of these died two months later, aged 53; four others had died outside an asylum, one of them after a second sojourn there; one lives in an asylum, again demented after having been at liberty for two years; seven died in an asylum where they had been returned; seven live in an asylum which they were never able to leave; thirteen died in the asylum, never having left it; two disappeared, and one of these was probably cured. Evaluating these results, the author concludes that in 64 per cent of the men with dementia paralytica who had been subjected to malaria therapy the results were unfavorable. After citing the later fate of the forty-two women with dementia paralytica who had received malaria therapy, the author shows that among these the frankly unfavorable results likewise amounted to 64 per cent.

Presse Médicale, Paris

46: 1209-1224 (Aug. 6) 1938

Effect of Fluid Diet and of Blood Loss on Development of Typhoid. L. Ambard, P. Barthelme and P. Mandel.—p. 1209.
*Acetarsone Therapy of Dementia Paralytica. L. Marchand.—p. 1211.

Acetarsone Therapy of Dementia Paralytica.—Marchand's report is based on the results obtained with acetarsone in the treatment of 111 patients with dementia paralytica. None of the patients treated were, or had been, subjected to malaria therapy. Three times a week the patients were given a subcutaneous injection of 1 Gm. of sodium acetarsone dissolved in 10 cc. of distilled water. The total for a series of treatments was 45 Gm. The series were separated by intervals of three or four weeks. In the first two injections only half of the dose, that is 0.5 Gm., was given, in order to test the sensitivity of the patient. During the first few weeks of treatment the patients were kept in bed. The number of series of treatments required varies in different patients. Some of the patients are able to leave the hospital after the first series. In some of the patients, in whom the dementia paralytica advanced rapidly, the author intercalated between the acetarsone injections an injection of quinine bismuth iodide until a gingival border appeared. Tests for syphilis were made on the blood and on the cerebrospinal fluid, before as well as after the treatment. The temperature was measured every day and the weight was determined before the treatment and then every month. An examination of the fundus oculi was made before the treatment and every two weeks thereafter. The author lists the results of the treatment in a tabular report. He says that he obtained "social recuperation" in seventy-one (64 per cent) of the 111 patients and improvement in ten patients (9 per cent); fifteen patients (13.5 per cent) died. The author speaks of "social recuperation" in those patients in whom the mental defects have disappeared so that they are able to resume their former occupations but who are not cured organically. The social recuperation was obtained in twenty-six patients after one series of treatments, in twenty-six after two series, in eleven after three series, in six after four series and in two after five series. Following a discussion of the behavior of the reactions in the blood and in the cerebrospinal fluid in the patients in whom social recuperation was obtained, the author discusses the relapses. He says that nine of these patients had to be hospitalized again, because of the recurrence of mental disturbances. The relapses are due to a premature arrest of the treatment, to an insufficiency of the doses or to excessive length of the intervals between the series of injections. The patients with dementia paralytica who have been treated with acetarsone should be kept under clinical and serologic control for several years after the treatment. The complications that may appear in the treatment with acetarsone are slight in comparison to the severity of the disease. Discussing the contraindications to treatment with acetarsone, the author says that the treatment should be avoided in senile subjects who present organic difficulties. However, tabetic symptoms and alcoholism without hepatic insufficiency do not constitute contraindications to treatment with acetarsone.

Sang, Paris

12: 677-780 (No. 7) 1938

New Applications of Karyoklasic Poisons to Experimental Pathology, Endocrinology and Cancerology. A.-P. Dustin.—p. 677.
New Method of Examination of Coagulability of Blood (Coaguloretractovisometry). L. Blacher.—p. 698.
*Hepatic Opotherapy and Cholesteremia: Experimental Study. P. Van de Calseyde.—p. 712.

Hepatic Opotherapy and Cholesteremia.—Van de Calseyde reports experimental studies on the effect of liver therapy on cholesteremia. Studies were made on human subjects as well as on animals. It was found that it is not possible to determine the antianemic power of liver preparations on the basis of the variations in the cholesteremia which they engender in normal human subjects and animals. There is no parallelism between the variations in the cholesterol content and the antianemic power of the extracts. Nevertheless the author thinks that his observations on the hypercholesteremia produced by the ingestion of whole fresh liver or of certain liver extracts used for the treatment of pernicious anemia is of considerable biologic interest. His investigations proved that the increase in cholesterol is not due to the factor that exerts the therapeutic action in pernicious anemia, to the cholesterol content of the liver or to the vitamin A content of the liver. The appearance of the increase in cholesterol after ingestion of hydrosoluble extracts prepared according to the methods of Cohn and Gänsslen seemingly indicates that the agent inducing hypercholesteremia is neither a lipoid nor a protein. Further investigations will be necessary to determine the chemical nature of the hypercholesterolizing factor of the liver. Other questions that await answers are: Is this substance present in tissues other than those of the liver? Is it related to the vitamins or hormones? By what mechanism does it increase the cholesterol content?

Annali Italiani di Chirurgia, Bologna

17: 525-666 (June-July) 1938. Partial Index

*Metabolism of Nitrogen and Chlorides After Injection of Normal Blood Serum of Horse. G. Conti.—p. 525.
Physical and Chemical Values of Blood in Experimental Burns. G. Prussia.—p. 543.
Influence of Intermittent Interruption of Arterial and Venous Circulation on Development of Renal Pyogenic Infection. P. Bassi.—p. 557.
Hemoperitoneum from Rupture of Nonpregnant Corpus Luteum: Case. S. Caminiti.—p. 639.

Metabolism After Injections of Horse Serum.—Conti observed the behavior of nitrogen and chlorides in the blood and of urea, uric acid and the chlorides in the urine of twelve normal persons who were given intramuscular injections of from 20 to 50 cc. of normal horse serum. The injections were administered at intervals of twelve hours until 140 cc. had been given. In all cases the injection was followed by increased azotemia, increased elimination of urea, uric acid and the chlorides in the urine and lowering of the chlorides in the blood. According to the author the results show that the proteins in the serum are disintegrated and eliminated shortly after the injection in a

similar manner to that which takes place in plasma proteins after transfusion. The results confirm the author's opinion that the plasma has a mechanical action on the blood, that the plasma proteins are disintegrated and eliminated shortly after transfusion and that disintegration of the erythrocytes takes place several days after transfusion with consequent liberation of erythrocytic proteins which are used by the blood. Assimilation of erythrocytic proteins reestablishes the equilibrium of the blood.

Bollettino, Milan

12: 85-148 (April-June) 1938. Partial Index

Early Diagnosis of Extrapulmonary Tuberculosis. A. Isella.—p. 93.
Isolated Fracture of Transverse Apophysis of Lumbar Vertebra: Case. M. Manfredi.—p. 105.
*Galvanocautery Puncture in Suppurative, Acute Lymphadenitis of Neck in Infants. G. Cigada.—p. 113.

Galvanocautery Puncture in Lymphadenitis in Infants.—Cigada reports satisfactory results from puncture by means of the galvanocautery in twenty-seven cases of either acute abscess or acute suppurated lymphadenitis of the neck. Both the therapeutic and the cosmetic results are satisfactory. The tiny scars left by the puncture are almost invisible and they disappear in a few months. Puncture by the galvanocautery has no contraindications. It is done without anesthesia. The perforations remain open all through the process of elimination of pus. It gives more rapid results than many of the other treatments commonly resorted to in these conditions. As a rule it suffices for complete elimination of the pus. The best results are obtained when the pus is in a circumscribed cavity or when the different cavities of an abscess are punctured and also when the pus is already near the superficial layers of the tissues. It is advisable to use galvanocautery needles of medium size in order to make well opened outlets for rapid and sufficient elimination of pus. Local hot applications and complementary treatments (vaccines) are indicated. The total number of perforations is from three to five. Only in rare cases is reopening of the perforations or a surgical incision necessary. The treatment is well tolerated by infants and children.

Policlinico, Rome

45: 1553-1592 (Aug. 22) 1938. Practical Section

*Action of Thymus on Blood and Spleen. S. De Candia and F. Floriani.—p. 1553.
Liver Lipolytic Enzymes in Therapy of Nutritional Diseases in Children. N. Amagliani.—p. 1556.
Epinephrine Treatment of Malaria. V. Romeo.—p. 1562.

Action of Thymus on Blood Formation.—De Candia and Floriani observed the behavior of the blood and of the spleen in twenty normal persons with normal sized spleen after an intramuscular injection of 2 cc. of thymus extract which contained 1 Gm. of fresh gland for each cubic centimeter of the extract. The observations were made during fasting. Determinations of the changes of the blood and of the spleen were made half an hour and one hour after the injection. The erythrocytes and the leukocytes, but principally the former, increased during the first hour. The leukocytic formula gave different results in various persons of the group. There was an increase of the monocytes and parallel diminution of the neutrophilic polynucleated leukocytes in some cases, moderate increase of either the lymphocytes or the neutrophilic polynucleated leukocytes in other cases and the leukocytic formula did not change at all in still other cases. In all cases the size of the spleen diminished during the first hour following the injection (3 cm. in the longitudinal diameter and 2 cm. in the transverse diameter) and the diminution lasted for more than an hour. In two groups of patients (the number of which is not specified by the author) suffering from either fibrous forms of splenomegaly (Laënnec liver cirrhosis, Banti's disease and bantiform syndromes) or malarial splenomegaly, they found that the size of the spleen did not change or had a slight change in fibrous forms of splenomegaly, whereas the injection induced a more or less energetic contraction of the spleen, which lasted for more than an hour in the group of patients who were suffering from malarial splenomegaly. The authors believe that the intramuscular injection of thymus extract can be used for the differential diagnosis between fibrous and malarial forms of splenomegaly. It can be used also instead of epinephrine in the treatment of malarial splenomegaly by means of repeated induced contraction of the spleen.

Archiv für Gynäkologie, Berlin

167: 253-396 (July 20) 1938. Partial Index

Pregnancy Intoxication Simulating Tabes Dorsalis. H. Offergeld.—p. 275.
Method of Testing Ecbolic Substances on Vagina of Rabbits. H. Runge, W. Beck and E. Hunt.—p. 284.
Tubal Pregnancy and Reaction According to Aschheim-Zondek. H. Klinkenberg.—p. 300.
Significance of Uterus and Adrenals for Luteinization. W. Wobker.—p. 339.
Interstitial Pregnancy. T. K. Andrianakos.—p. 343.
*Proliferation of Uterine Mucosa in Case of Intra-Uterine Administration of Estrogen. P. Grumbrecht and A. Loeser.—p. 373.
Significance of Vegetative Nervous System for Incretory Function of Anterior Lobe of Hypophysis. L. Herold and G. Effkemann.—p. 389.

Intra-Uterine Administration of Estrogen.—Grumbrecht and Loeser say that experimental studies on the pathology and therapy of ovarian insufficiency revealed that the requirements for the action of estrogen on the various organs differ considerably. For instance, whereas the castration atrophy of the sex organs can be counteracted by the parenteral administration of estrogen, the changes which castration produces in the thyroid can be counteracted only if the substance is administered by way of the uterus. If it is administered by any other than the uterine route, it exerts no influence on the thyroid. The authors studied the reaction of the uterus to the local application of various estrogenic substances. They made experiments on infantile rats and guinea pigs and on mature rats. They found that the intra-uterine application of different estrogenic substances produces proliferation of the uterine mucosa with smaller doses and in a much shorter time than is the case in subcutaneous administration. The observations in the course of the animal experiments suggested to the authors the possibility of the clinicotherapeutic utilization of the intra-uterine administration of estrogen. For use in human subjects they employed suppositories which were from 4 to 5 cm. in length and a few millimeters in thickness. Each suppository contained 500 international units of estrogenic substance in a base of theobroma oil. The suppositories were sterile and were stored on ice. The authors say that their introduction into the internal uterine os was not difficult. In order to prevent the slipping back, a strip of gauze was introduced into the cervical canal for three or four hours. With this mode of application, undesirable complications such as increase in temperature, pains or local irritations were avoided. The case histories reported by the authors indicate that the intra-uterine administration of estrogenic substance is effective in cases of hypomenorrhea and secondary amenorrhea and in uterine hypoplasia with ovarian insufficiency and oligomenorrhea.

Deutsche Zeitschrift für Nervenheilkunde, Berlin

147: 1-136 (July 18) 1938

*Symptomatology and Pathogenesis of Lumbosacral Neuritis. H. Pette and P. E. Becker.—p. 1.
Myoclonic Syndrome in Amyotrophic Lateral Sclerosis. G. Doring.—p. 26.
Electromyographic Investigations on Thomsen's Myotonia and Dystrophia Myotonica. W. Eichler and I. von Hattingberg.—p. 36.
Head's Zones. H. Plügge.—p. 78.
Observations on Reduction of Muscular Activity in Myasthenia Gravis. W. Birkmayer.—p. 118.

Lumbosacral Neuritis.—Pette and Becker show that lumbosacral neuritis is a definite disease entity. On the basis of nine selected cases, they demonstrate the different forms the disease may take as regards the symptomatology and the course. The subjective and objective symptoms indicate that the morphologic changes, although as yet they have not been verified by anatomic studies, are chiefly in the region of the sympathetic centers and tracts. The clinical aspects, together with the somewhat characteristic changes in the cerebrospinal fluid, suggest that the disorder is an inflammatory process of spinal ganglions in the region of the lumbosacral plexus. Accordingly the authors designate it as a neuritis of the lumbosacral plexus. The disorder is closely connected with herpes zoster, they say, and consequently it can be classified with the group of virus diseases of the nervous system. The as yet hypothetic causal agent is characterized by neurotropic properties. As in other virus diseases of the nervous system (poliomyelitis, rabies), the term neurotropism is applicable in its restricted sense in lumbosacral neuritis. From the fact that a predisposition to so-called

rheumatic disorders and to excessive sympathetic reactions is frequently observed not only in the patients themselves but also in members of their families, the authors conclude that constitutional factors play a part in the pathogenesis of lumbosacral neuritis.

Münchener medizinische Wochenschrift, Munich

85: 1137-1176 (July 29) 1938. Partial Index

Question of Existence in Germany of an Encephalitis of the Character of Encephalitis Japonica. H. Pette.—p. 1137.
Pathogenesis of Scarlet Fever in Persons Who Have Not Been in Contact with Scarlet Fever Patients. W. Schultz.—p. 1140.
*Types of Diphtheria Bacilli and Clinical Course of Diphtheria in Children. S. Werner.—p. 1141.
Observations on Kala-Azar in Children in Province of Argolis in Greece. S. D. Kirimlidis.—p. 1143.
Deficiency of Vitamin B_1 or Rheumatism. A. Nemecek.—p. 1147.
*Angina Pectoris with Fatal Outcome Elicited by Inhalation of Hydrogen Sulfide Gas: Case. A. Hellfors.—p. 1149.
Neurology and Neurosurgery of Angina Pectoris. H. Jessen.—p. 1149.

Types of Diphtheria Bacilli and Course of Diphtheria.—Werner says that among 134 cases of diphtheria in which the type of bacillus was determined there were eighty-four cases with the type gravis, forty-two cases with the type intermedius and eight cases with the type mitis. A relationship between the course of the disease and the type of the diphtheria bacillus could not be detected. There was no evidence that one type of bacillus would cause a severe form of diphtheria and another type a mild form. A change in the type of bacilli was observed in 9.7 per cent of the children; in all others the same type of bacillus was detected throughout the entire course of the disease. It was not possible to furnish definite proof of a real change in type. Since the available space did not permit a segregation of the patients according to the type of bacillus, there was always a possibility of superinfection with another type of bacillus. The persistence of positive smear tests was considerably longer in the patients in whom the gravis type of bacillus was present than in the patients with the intermedius type.

Inhalation of Hydrogen Sulfide Gas.—Hellfors reports the history of a man aged 63 who had angina pectoris after he had inhaled hydrogen sulfide gases while he was conducting experiments. In response to treatment the attacks of angina pectoris subsided somewhat but they recurred after renewed exertion. Then the patient contracted influenza, in the course of which the angina pectoris was aggravated. He died in a severe attack of angina pectoris. On the basis of this case history, the author suggests that the angina pectoris-like pains which are observed in persons with similar intoxications are due to temporary circulatory disturbances in the coronary vessels. He admits that two brothers of this patient likewise had angina pectoris, but he nevertheless thinks that the hydrogen sulfide intoxication was the eliciting factor of the angina pectoris in the reported case, because fourteen months previously the patient had a slightly increased blood pressure but no signs of coronary disease.

Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam

82: 3647-3718 (July 23) 1938. Partial Index

*Blood Group and Diameter of Erythrocytes. Tjiook Kiem Bok.—p. 3657.
Echinococcus in Central Nervous System. M. Weersma.—p. 3662.
Anterior and Posterior Rachischisis. A. J. P. Van Den Broek and S. Van Dam.—p. 3666.

Blood Group and Diameter of Erythrocytes.—Tjiook Kiem Bok was induced to investigate a possible relationship between the blood group and the mean diameter of erythrocytes by a report of Pijper, who in studies on forty-eight cases was believed to have found evidence of such a relationship. Tjiook Kiem Bok made his tests on 500 healthy persons (students, nurses and laboratory staff). He determined the four classic blood groups and the mean diameter of the erythrocytes, respectively, by the method of Moss, Lee and Vincent and the diffraction method, using Pijper's blood cell tester. From this investigation the following conclusions could be drawn: 1. A correlation between blood group and red cell diameter, as Pijper assumed, could not be demonstrated. 2. The mean diameter of the erythrocytes of these persons is 7.3 microns, with a normal range of from 6.8 to 7.9 microns. 3. Sex has no influence on the mean diameter.

Nordisk Medicinsk Tidskrift, Stockholm

16: 1125-1164 (July 16) 1938

*Boeck's Iritis. G. Østerberg.—p. 1125.
Electric Shock: Significance of Different Technical Factors and of Individual Resistance in Accidents Due to Electric Shock. H. Ihde.—p. 1132.
Simplified Method for Diagnosis of Pregnancy According to Kapeller-Adler. N. Nielsen.—p. 1144.

Boeck's Iritis.—Østerberg describes the case of a girl, aged 14, in whom a torpid, indolent monocular nodulous iritis developed and in the course of a year reduced the vision to 2/50 and threatened perforation of the eye. Enucleation was contemplated. There were no pulmonary symptoms but the roentgenogram of the lungs resembled a miliary tuberculosis and operation was deferred. In the course of nine months spontaneous recovery of the eye occurred, with restoration of vision and of the exterior of the eye almost to normal, and spontaneous regression of the pulmonary changes. Microscopic examination of tissue from an apparently healthy tonsil demonstrated sarcoid of Boeck. The author asserts that there is a distinct Boeck's iritis which is not identical with iritis tuberculosa; it is less painful, less destructive and more prolferative than iritis tuberculosa. The differential diagnosis must be based on the patient's general condition and the tuberculin, roentgen and microscopic examinations. Iritis is a relatively rare symptom in Boeck's disease, occurring in from about 5 to 10 per cent. Twenty-seven cases of Boeck's disease with iritis are tabulated from the literature.

Ugeskrift for Læger, Copenhagen

100: 749-776 (July 7) 1938

Hand-Schüller-Christian Syndrome: Case. E. Warburg.—p. 749.
Monocytic Leukemia (Reticulo-Endotheliosis): Three Cases. P. Plum and S. Thomsen.—p. 755.
*Solitary Nonparasitic Hepatic Cysts. I. Baumgarten.—p. 762.
*Heerfordt's Syndrome (Uveoparotid Fever), Manifestation of Boeck's Sarcoid. M. Jersild.—p. 765.

Solitary Nonparasitic Hepatic Cysts.—Baumgarten says that about 100 cases of solitary nonparasitic hepatic cysts have been reported in the literature since 1864. The majority of the cysts are caused by retention in the bile ducts, due to congenital malformation or to local obstruction of small intrahepatic bile ducts. Most of them give no symptoms. If symptoms do occur, they are usually due to pressure on neighboring organs. Exact diagnosis is rarely made before operation or necropsy. The only effective therapy is surgical intervention, and the ideal operation is extirpation. The highest operative mortality occurs in cases in which puncture is done, the lowest in radical operations. In the case reported, in a woman aged 26, extirpation of the cyst was followed by recovery.

Heerfordt's Syndrome.—In Jersild's two cases of Heerfordt's syndrome the roentgenologic changes in the lungs led to the diagnosis of sarcoid of Boeck. In spite of the extensive processes the patients felt remarkably well and the Mantoux reaction, as frequently described in cases of sarcoid of Boeck and Heerfordt's syndrome, was positive only on larger doses of tuberculin. In one case with exanthem, biopsy supported the diagnosis. The author suggests that, since the etiology of sarcoid of Boeck is not clear, the relation of the disease to uveoparotid fever, which generally appears as an infectious disease with acute onset, may open new perspectives. Heerfordt's syndrome, he says, is surely the initial stage in a long-continued chronic infectious disease.

100: 777-806 (July 14) 1938

*Investigations on Etiology of Epidemic Hepatitis. T. T. Andersen.—p. 777.

Etiology of Epidemic Hepatitis.—Andersen asserts that jaundice in swine, contrary to the common conception, is a parenchymatous liver disorder corresponding to hepatitis in man and is transmissible to other swine and other animals, which demonstrates the infectious nature of the disorder. His investigations also show that hepatitis in swine probably originates from a similar latent infection in rats. Since there is hepatitis in swine and since, according to statistical studies, an alimentary infection is probable in man, he is inclined to believe that hepatitis in swine is one of the causes of hepatitis in man and is in Denmark presumably the most important cause.

THE STUDENT SECTION

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Obstetric Education

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CHICAGO

The practice of medicine in America has been the subject of discussion, praise and criticism during the past few years perhaps to a greater extent than during any previous comparable period of time. At no time in our history have American physicians been so aware of the interest of the people in the quality and quantity of medical services available.

The interest always manifested in the illness and death of mothers and infants has resulted in numerous studies of the underlying factors causing the maternal and infant mortality in different parts of the United States. The results of these studies made by medical specialists in their respective fields have been constantly brought to the attention of both the medical profession and the public.

The White House Conference in 1930 studied all phases of the problem and published many volumes which are valuable sources of factual information. Following the exhaustive study of maternal mortality in fifteen states made by the Children's Bureau, maternal-mortality surveys were made in many states and in many of the larger cities in the United States. The results and conclusions of all these studies are remarkably alike. Analyses have been made of all factors concerned in maternal mortality, and the responsibility assigned to the physician has not been small. The fact that lack of judgment or negligence on the part of the physician is responsible for a portion of the maternal deaths in the United States has caused not a little concern but has resulted in few constructive programs for improving the situation. In the last generation there has been considerable improvement in the care received by maternity patients in this country, but this improvement has not kept pace with that of most of the other medical specialties.

The art of obstetrics has been considered strictly as a part of medical practice in the United States and without doubt it will continue to become increasingly so in the future. No one who is familiar with the high professional standards of the medical profession in the United States doubts that the average physician practicing obstetrics renders service to the best of his ability and knowledge. Since the quality of obstetric care received by a patient depends primarily on the amount and type of education and experience her physician has had in this specialty, we are concerned primarily with a consideration of these subjects. There can be no doubt that if every physician practicing obstetrics had a thorough basic knowledge of antepartum care and of the conduct of labor there would be fewer tragedies of childbirth.

The Council on Medical Education and Hospitals of the American Medical Association reported in 1937 that "the teaching of obstetrics is at a lower level than that of the other major clinical departments. Comparatively few schools offer to their students an adequate practical experience under competent supervision. This may result from a variety of causes, one of which is, undoubtedly, the failure of administrative authorities to provide access to a sufficient amount of clinical material. Another may be the feeling on the part of teachers that the practice of obstetrics should be reserved for specialists and that therefore the ordinary undergraduate does not need much training along this line."

Eight years ago the White House Conference Committee on Obstetric Teaching and Education stated that:

> The better the clinical training of students in the art of obstetrics, the better obstetrics they will practice, and this in turn will be reflected in improved results. . . . The need is not for less theory but more clinical instruction. . . . In so far as obstetrics is concerned, the majority of students at the time of graduation are not qualified to assume the responsibilities of caring for maternity cases. . . . They may have had in most instances sufficient theoretical training but they lack actual experience. It is obvious, then, that obstetric educational facilities in this country have been entirely inadequate in so far as the teaching of actual delivery care is concerned. There have been and still are too few well organized women's

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clinics in connection with medical schools to give the necessary training and experience to medical students, to say nothing of the dearth of facilities for developing specialists in this field.

Few medical schools today have sufficient clinical obstetric material available for the instruction and training of their students in antepartum, delivery and postpartum care. The importance of such instruction and training is illustrated by the fact that in a Midwestern state, according to a recent survey, more than 50 per cent of the physicians include obstetrics in their practice.

Dr. W. C. Danforth, chairman of the Illinois Committee on Maternal Welfare, wrote in 1936:

> The ideal remedy for the high maternal mortality in this country would be to provide obstetric attendance and well equipped hospitals in which women in labor may be cared for. This ideal state of affairs will not arrive for a long time but gestation and labor will continue.
>
> Some attempt must be made to improve the present conditions while we wait for the changes which time will no doubt bring. For many years, in any event, most of the women in the majority of our states will continue to be cared for by general practitioners. It is not fair to demand of the man in family practice the same familiarity with and skill in the handling of all the obstetric problems which are sometimes presented. He must also meet medical problems in many other fields, and the incessant demands upon his time, if he is a successful practitioner, make a minute knowledge of any special field impossible. In many communities, in our own state as in others, the general practitioner may be compelled to meet situations which would tax the skill of the specialist in his fully equipped hospital, assisted by a trained personnel. Without special knowledge, lacking trained assistance and the material resources of a hospital equipped to deal with obstetric emergencies, he cannot be too greatly criticized if, in some cases, his results are not ideal. He must, however, have sound fundamental knowledge of obstetrics and realize not only what it is wise to do but also what it is unsafe to attempt.

Before considering what changes might be desirable in obstetric education, let us review a few facts concerning the education now provided.

A recent Children's Bureau questionnaire answered by 2,538 graduates of sixty-one medical schools in 1936 revealed that with regard to the study of obstetrics:

> Lectures were begun by 44 per cent in the second year.
>
> Lectures were begun by 55 per cent in the third year.
>
> Clinical training was begun by 4 per cent in the second year.
>
> Clinical training was begun by 70 per cent in the third year.
>
> Clinical training was begun by 25 per cent in the fourth year.

Practically 100 per cent reported that their clinical training included examination and care of women during pregnancy, labor and the postpartum period. This survey shows that didactic and clinical obstetric teaching begins during the second or third year in most medical schools; it does not, of course, reveal the amount of instruction given or the knowledge of the instructors of the principles of obstetrics as applied to actual practice. As Dr. Weiskotten pointed out in his survey of medical schools: "It would appear that in many instances far too little attention has been given to the selection of the faculty. It is safe to assume that a teacher should have some special preparation and that an individual who has had no such training or experience in a subject is not competent to teach it." The failure of some schools to teach students how to practice obstetrics in the best interests of their patients under the conditions they must work under in homes and in small hospitals is responsible in no small part for their difficulties in later practice.

STUDENTS' CLINICAL EXPERIENCE

Concerning their clinical experience while in medical school, the 2,538 recent graduates reported the facts presented in table 1.

The "Essentials of an Acceptable Medical School," approved by the House of Delegates of the American Medical Association, states that every medical student should have actual charge of fifteen maternity patients under the supervision of a clinical instructor, yet 19 per cent of these students delivered no patients in hospitals and 27 per cent had no home deliveries as part of their training. Fifty-nine per cent of the students had a total of twenty or fewer deliveries in hospitals and homes. Twenty-three per cent of the students reported delivering ten or fewer patients in hospitals and homes.

The number of patients a student delivers is in itself no indication of the clinical training received, for without competent instruction and supervision the experience is of little value. However, with so few actual deliveries by students it is obvious that the amount of experience and instruction must be extremely limited for a large proportion of the students.

According to the "Essentials of a Hospital Approved for Training Interns," prepared by the Council on Medical Education and Hospitals of the American Medical Association in 1935, an intern should deliver at least ten patients while in the service. Concerning their obstetric experience during internship, the recent graduates referred to reported the facts given in table 2.

Twenty-two per cent reported delivering ten or fewer patients in home and hospital during their internship.

Thirty-two per cent reported delivering twenty or fewer patients in home and hospital during their internship.

Of the interns who attended hospital deliveries, 22 per cent reported that their deliveries were not supervised by an obstetrician.

Seventy-two per cent of these graduates plan to include obstetrics in their practice and 15 per cent plan to specialize in obstetrics. Eighteen

per cent of them did not believe that their obstetric training in medical school and during internship qualified them to include obstetrics in their practice. Sixty-three per cent of them wished to receive more obstetric training, and 23 per cent reported that they were unable to do so because of too few hospital appointments in this field.

There are only eighty-eight approved hospitals in the United States admitting more than a thousand patients annually which offer residencies in obstetrics or obstetrics and gynecology. Only forty-three of this number offer both resident and assistant resident positions. In these hospitals there are only about 150 resident or assistant resident appointments in obstetrics and obstetrics and gynecology made each year.

TABLE 1.—*Deliveries by Medical Students*

Number of deliveries	0	1-10	11-20	More Than 20
Percentage of students delivering this number in hospitals	19	49	17	15
Percentage of students delivering this number in homes	27	43	22	8

One inescapable conclusion of this questionnaire study of obstetric education is that the average physician entering practice today does not have sufficient clinical training in obstetrics to recognize and treat competently the many complications that may arise during pregnancy and labor. The importance of this conclusion is emphasized by the limited number of specialists in obstetrics, most of whom are concentrated in a few large cities.

GRADUATE STUDY

Attempts to provide postgraduate lecture courses in obstetrics for local practicing physicians have accomplished little more than to make the individual physician realize more than ever his inability to provide competent obstetric care. There has been a great demand from these physicians for opportunities to return to clinical teaching centers for further training. Most of them have been disappointed, for there are few places where they may go for such training. Opportunities for practicing physicians to return to the larger teaching hospitals have been provided to a certain extent in several states and an increase in the number of these may be expected in the near future.

The problem confronting certain medical schools is the difficulty in making sufficient clinical obstetric material available for all the students. This lack of teaching material cannot be remedied easily, if at all, in many medical schools.

The establishment of a few maternity centers primarily for teaching purposes in selected areas, especially in the South, would provide opportunities for additional clinical training for many students and practicing physicians. These maternity centers should provide care for the medically indigent patient and afford opportunities for research, and should be supported by public funds. The greatest difficulty in establishing such centers would be encountered in staffing them with instructors who are willing and competent to teach sound, conservative, routine obstetrics rather than to demonstrate their surgical skill or unusual cases of great interest to them but of little practical teaching value.

In order to provide competent medical care for a larger proportion of maternity patients, either there must be greater opportunity for obstetric training before graduation and during internship, or the practice of obstetrics must gradually be limited to those men who have had opportunities for special training in obstetrics subsequent to their ordinary internship. Every effort should be made to increase the number of resident appointments in hospitals with maternity services and to secure the services of the best obstetricians in the community to teach and supervise the work of the interns and residents.

Whatever progress in obstetric education is to occur in the near future will depend to a great extent on the study and careful consideration by every one concerned in the teaching of obstetrics of (1) the instruction and training now given medical students and graduates and (2) the results of the services these physicians render their patients when in practice.

The importance of adequate instruction for undergraduate and graduate students has been recognized and stressed by teachers of obstetrics for many years. Unfortunately the tremendous social importance of such instruction is not recognized by teachers in other medical fields and by the administrators of medical schools who listen to but do not act effectively in carrying out programs of obstetric education advocated by teachers of obstetrics.

TABLE 2.—*Deliveries by Interns*

Number of patients delivered	0	1-10	11-20	More Than 20
Percentage delivering this number in homes during internship	82	13	2	3
Percentage delivering this number in hospitals during internship	15	9	10	66

If obstetrics is to maintain its position as a recognized medical specialty in the United States, our physicians must receive sufficient undergraduate and graduate training to enable them to guide their patients safely through pregnancy, to conduct deliveries with the skill and judgment required, and to recognize the value of expert consultation when complications arise.

Comments and Reviews

THE ART AND TECHNIC OF STUDY

Thousands of students are at present returning to medical schools throughout the United States to continue their studies or to engage in the study of medicine for the first time. Each one of the various medical curriculums will require of the students great concentration of effort and continuity of attention. In this long process the students naturally will acquire habits of study, and it seems desirable for them to be guided by certain general principles which may increase their efficiency and make more effective the hours of study. Such is the intention of the following opinions of some writers who have given special attention to the technic of study.

Walker [1] points out that medical students are far too ready to slump into a condition of subnormal physical health. A reaction tends to set in early against the athletic activity of the public schools when undergraduate life is reached, but sound physical health must be maintained. The rich opportunities given by university life for the preservation of physical fitness should be exploited fully. A certain proportion of each week and each year should be set aside exclusively for recreation. Of equal importance is the development of mental stamina, which term includes not only the acquisition and maintenance of will and judgment, remote alike from rashness and pusillanimity, nor merely the ability to sacrifice the present to the future, but also the cultivation of the gentler arts of the world. Medicine may be a jealous mistress, but he who gives her his all will never experience the contentment and philosophical security which a broad general culture imparts. During the student years, time must be found for the study of a science for its own sake—any subject which appeals to the individual—or for the cultivation of literature or an art. The necessity for travel in the student years must be mentioned. During these tours, either at home or abroad, there can be no harm in visiting the hospitals and schools; but any attempt at promiscuous study, Walker believes, should be suppressed.

In the study of medicine much knowledge has to be acquired in a relatively short time. While it is necessary to know, for example, that the islets of Langerhans are not in Polynesia, loading up with necessary facts is by no means the most important part of the curriculum. Much more important is the acquisition of technical skill, dexterity, practical experience and clinical acumen. Of greater importance still is the keeping of a proper perspective during the various stages of the curriculum. In practical work and in reading, every student should examine his methods of study periodically, ruthlessly scrapping unprofitable habits and customs.

READING AND PRACTICAL WORK

Walker believes that reading should be done in the evening. The student should consider the technic of reading. At the outset, the student should decide whether he remembers best by merely looking at a written word, by writing it down or by hearing it spoken. That is, he should learn whether he has a "visual memory" or an "auditory memory." The former fortunately is more common. Every student must investigate his powers of memory by actual experiment, decide his own classification, and work on it. Once the most favorable channel for the reception of facts is decided, the details of study can be regulated. Study from books should be done in privacy in an environment conducive to alertness and clarity. Anything conducive to too much physical comfort must be shunned. No attempt should be made to read soon after a meal or when tired. Reading in the train or bus or "at any old time" is a waste of energy and promotes staleness. As a general rule, it is said that, if the practical work of a working day has been faithfully performed, two hours' book work in the evening is ample. It is then that reading should consolidate and fix the practical work done during the day.

Walker believes it should be an inviolable rule that whatever has been seen or heard in the lecture room, laboratories or wards during the day should have first claim on the time available for reading during the evening. Surgery must be read during the performance of surgical appointments, ophthalmology while the student is actually seeing ophthalmic patients, and so on. It is worse than useless to attempt to acquire the formal dogmas of medicine by suddenly beginning at page 1 in a large textbook. The greater part of each morning and afternoon should be devoted to practical work and training. The surpassing value of dissection, of study in the wards, outpatient department and receiving room, of lectures which flavor facts with a lecturer's personal experience, and particularly of the "writing up" of patients' records, needs no emphasis. It may be taken for granted that a "part" once thoroughly dissected is etched deeply in the memory. Similarly, a scientific or clinical investigation once thoroughly per-

1. Walker, G. F.: The Technic of Study, Lancet 2: 481 (Aug. 31) 1929.

formed repays the investigator many times over by conferring ineradicable knowledge. In dissecting, the student should display the region so that he can subsequently recall it in three dimensions. And in investigating patients, when once the full straight facts have been clearly displayed, the imagination should be invoked to illuminate the patient's own side of the problem. For the precise and formal extraction of data about a patient, there is no more pithy and significant advice than the exhortation "Look and see." The cultivation of sincerity and the preservation of an ever open mind should be comprised in that advice.

The technic of practical study needs as much watchful care as does the technic of reading. It is very easy during the clinical years to be in a place where work can be done, should be done, and is in fact being done—by others. The tendency to lapse into intellectual somnolence during demonstrations is insidious in its onset, but a habit of vigorous enthusiastic attention is not difficult to acquire and when once acquired is seldom lost. The mere acquisition of the habit is worth while for its own sake; its utility will probably outlive the utility of many of the topics to which it is first applied. A large teaching hospital usually abounds in places where dawdling is possible and prevalent.

Here are two little pieces of advice. First, the midday meal should be taken free from "shop." Secondly, the notebook is worth consideration—a good small loose-leaf notebook should accompany the student through his whole curriculum. It should be just small enough to fit in the pocket, it should be available at all times, and each night it should be tidied up and full pages withdrawn to be placed in appropriate accumulations.

The Course as a Whole

The really fundamental thing to grasp is that the course is a whole, and not a string of loosely connected segments each requiring a concentrated onslaught with subsequent relegation to the background. I do not mean, Walker says, that a student should attempt to go forward three steps at a time but that he should look on his curriculum as a series of phases of initiation into the science and art. Each phase prepares the student for subsequent phases but is very dependent for its full consummation on preceding phases. To reduce this to practical terms it may be said, for example, that anatomy and physiology should forthwith be continuously studied during clinical work.

It follows from the fact of the unity of the course that the textbooks of each phase should be retained and kept viable during subsequent phases. Revision and maintenance of knowledge is safer and easier if done from the actual pages of the big textbook used during the phase when it was intensely studied. "I say big textbook, because one big textbook should be selected for each topic and adhered to from start to finish. The small summaries and cram books have their place, but they are mainly useful as a help to marshal facts. The author of a most successful synopsis, far from making the usual claim to be meeting a 'long-felt want,' says in his preface that ultimate reliance on anything but the larger books will lead to failure. Just as the textbooks of successive phases should be carefully retained throughout, so must the microscope not be sold. I do not mean that the shelves should be laden with large textbooks on the history of medicine, but the bald facts of study can be enlivened by reference to an encyclopedia when a proper name is found. And from time to time monographs should be perused."

Examinations

It is useless to ignore the fact that examinations loom large in the curriculum. "I have many times told my student friends that the examination incidents—and I am convinced that 'incident' is the right word—should be happy episodes. This information has always evoked incredulity, but on several occasions graduates have subsequently admitted personal verification. Of course, only fools make light of examinations. They should be taken so seriously that the student, as soon as he enters a particular phase, should plan his work for the terminal examination of that phase by actual time-table and schedule. He should record diagrammatically his progress through the phase so that the work is spread evenly over the time available. As an example let us suppose that a phase of study in one of the ancillary subjects lasts six months and that the textbook concerned has 500 pages. Then 100 pages must be covered each month by schedule, the actual pages being selected each evening according to the nature of the particular lecture, demonstrations and practical work enjoyed during the day. The art of passing examinations consists in doing steady comprehensive work during the whole of the antecedent phase. He who works steadily in the practical work of a phase with concurrent systematic reading cannot be 'plowed.'"

Brief Rest Periods

It may be practical to review the psychologic data whose interpretation may facilitate study, as has been done by Gillespie [2] at Guy's Hospital in London. It is found, he says, to be beneficial

2. Gillespie, R. D.: The Art of Study: Its Principles and Their Application, Brit. M. J. 2: 365 (Sept. 1) 1928.

if brief rest pauses are introduced at intervals during long periods of work. Thus not only may mental work be made more efficient but the output of factories has been favorably influenced. It is usually considered that to transfer one's attention to another task after feeling fatigued at a previous one is efficacious in restoring mental efficiency. The so-called "subjective fatigue," which is another name for boredom, tends to be abolished in this way. Mental fatigue is a matter of comparative unimportance. Only a small part of it is probably attributable to cerebral activity, and even this part is readily abolished by a rest pause or by normal periods of sleep. The greater part of mental fatigue is made up of boredom or by the so-called "specific objective fatigue," which is surmounted by changing over to another type of mental activity. The apparent mental incapacity in cases of "mental exhaustion" is nearly always the result not of intellectual effort but of anxiety or some other emotional disturbance, resulting from preoccupation with some personal problem. This is dramatically illustrated in the sudden recovery of persons complaining of "brain-fag" which has perhaps limited their work to periods of less than an hour each, when a source of worry is removed. Gillespie says that for practical purposes the mind is almost tireless. Even when there is considerable deprivation of sleep, intellectual work may be persistently maintained at a high level if the worker does not worry about his insomnia.

Outside Interruptions

There is a factor called "warming up" that occurs as the task proceeds. Our mental machinery seems to have a degree of inertia which can be overcome only gradually. Hence the importance of avoidance of outside interruptions. To be called away to a telephone causes a greater loss in efficiency than is indicated by the mere loss of time; the amount of work done immediately after such an interruption is less than the output immediately before the interruption. It is desirable, therefore, to arrange work in such a way that it can be carried on without interruption for several hours at a time if need be. Much of the most difficult part of a difficult study is the beginning of it. A careful arrangement of very brief rest pauses will increase the total mental output, but the distribution and length of the pauses have to be worked out empirically by each individual for the type of work that he does.

Memory is one of the most important aspects of the mental process involved in study, but mere memory in the sense of physiologic retentiveness is not enough. To have it in a high degree is an asset, but unless its stores are usable in an intellectual way a phenomenal memory may even be a hindrance. The author cites an experiment which seems to show that the last night's cram before an examination is of little benefit unless for the acquisition of entirely new material. We lose only slightly by abstaining from all work in the last few days before an examination and probably gain considerably in that elusive quality called "freshness."

In merely learning anything by heart, certain devices are of value. Grouping the material to be learned into intelligible unities naturally occurs to every one; presence of rhythm makes learning easier. It is easier to learn poetry than prose. It has also been found experimentally that, if a poem of several verses has to be memorized, it is more economical in the long run to learn it as a whole rather than stanza by stanza. We remember best what interests us most. Interest reduces also the effort both of attention and of remembering, and it increases the powers of observation as well. Interest leads also to selection and under its influence we select what we wish to remember often without realizing it.

But not everything, Gillespie says, should be left to this instinctive selection. With some people there is too much slavish routine reading, too much of plowing through masses of perhaps unnecessary and irrelevant textbooks, omitting nothing lest anything be missed, as some people read every page even of the inferior works of fiction produced by a good author.

Memorizing

There is no evidence for the statement, sometimes heard, that everything seen or heard or done is retained and that nothing is ever completely forgotten. Consider what would happen if we did not, practically at least, forget much of our experience. In recalling some event we would revive the smallest details and its recollection would require as much time perhaps as the event itself, and thus we would hardly have time available to register new impressions. Memory then is selective. The best memory is possessed by the man who makes the greatest number of associations with his experience; but the most effective memory is a combination of associative richness with selection. The man who thinks about his experience has much the better memory, and this marks the distinction between crammed information and real knowledge of the subject.

There are methods whereby association can be multiplied, and some of them are by discussion and debate and by reading different books in the same field, and also by writing

about the subject. Writers of textbooks and monographs frequently acknowledge that the persons to whom the writing has been most beneficial has been the authors themselves. It is not possible to write about every topic while preparing for an examination. A valuable exercise is the writing of papers, and they need not be necessarily on original work. It is good for the student to read regularly one of the current general medical periodicals, together with occasional issues of the more specialized journals. After graduation, the first few years often have to be spent by the young medical man in ridding himself of the unquestioning faith in authority and in the printed work that he has acquired during the student days, and of the parrot-like habits of memorizing rather than understanding.

The methods of study adopted must vary with the individual and with the nature of the subject. Some stress the regularity of habits of study, as a habit can thereby become established which has a certain dynamic effect of its own.

Incentives to Study

The subject "Incentives to Study" came to the attention of the Yale University student body a few years ago and found expression in a survey. A questionnaire was sent to each undergraduate and about 50 per cent of the total student body returned answers. Reviewing the summaries of this survey, Davis [3] reaches the following conclusions: (1) Definiteness and direction of purpose become incentives to study; (2) concentration, rather than distribution, should be the curricular desideratum; (3) superior motivation placed Yale's poorer students in the lead in scholarship, but excessive financial handicap may overcome motivation; (4) it is the student's belief that for honor men the two final college years should be wholly tutorial; and these tutors should be the greatest teachers, instead of such men being reserved for the large lecture courses.

Process of Study

The following steps in studying any definite section of a subject are suggested by Ryerson of the University of Toronto: (1) collection of data, (2) selection and organization, (3) assimilation.

Data may be collected by the student from any source available. Selection and organization involve judging and condemning so-called facts, then dividing ideas into groups. Deductive reasoning descends from the general to the particular, while inductive reasoning separates the relevant from the unimportant. Safety and skill in neglecting some and accepting other facts may be developed by proceeding from the principal thoughts to the details. The central idea must be found and firmly gripped. Principal thoughts must be searched for and recalled frequently for valuation. All articles should progress by groups of facts.

Assimilation is getting nutriment into usable form to accomplish a purpose. Ideas are recalled by their relation or connections with other ideas.

Individuality must be realized, the power to work must be developed, and system should be cultivated. Concentration of attention is to be acquired to eliminate waste.

3. Davis, James E.: Teaching and Learning, J. Michigan M. Soc. 35:311 (May) 1936.

MEDICAL PRACTICE OF THE FUTURE

What is it that leads men to enter the medical profession? In most cases the modest goal is that of earning an honorable living. Some cherish the ambition of contributing to the advancement of medical science, others the still loftier aim of serving their fellow men. An astute minority strives for personal aggrandizement and for the all too rare distinctions allotted to medical men. Whatever our initial impulse may have been, we have embarked on a swiftly flowing stream with many currents and hidden rocks. We should realize these hard facts. Considering all the circumstances of its past environment, the products of our orthodox system of education have been wonderfully good. Tradition is sometimes a valuable stimulus; on the other hand, it may act as a drag on imagination and progress. Under our present social and educational régime, an increasing proportion of bright young men and women throng our higher schools and universities, and in due course they swell the crowded ranks of the medical profession. Graduates are now turned out by mass production, more or less standardized and polished, like motor cars belonging to a particular factory and, like motor cars, tending to become out of date when compared with later models.

The young graduate, once he has secured his diploma of proficiency, usually has a transient wave of optimism. He soon discovers that he has fallen out of the frying pan of undergraduate life, even if supplemented by postgraduate experience, into the fire of everyday practice with new responsibilities and anxieties. He finds that the environment and equipment required for successful family practice are utterly different from the hospital conditions in which he has been trained. This is not strange, since few of his teachers have been through

Abstract of an address delivered by Sir James Purves-Stewart before the University of Leeds Medical Society, Edinburgh M. J. 45:309 (May) 1938.

the mill of general practice. The common diseases for which he is now consulted are unlike those dramatic clinical pictures on which he concentrated his attention in hospital wards and theaters. He comes to realize the truth of the aphorism that "there is no such thing as a disease; there is only a sick person," and that his success largely depends on studying and dealing with the personalities of his patients.

His primary problem is usually economic. A few lucky young graduates find comfortable practices awaiting them. The more brilliant students may be attracted to teaching or to research; others may undergo further training with the intention of qualifying as specialists. The majority are content if they can find congenial employment and economic independence. Even in England the supply of medical graduates is already becoming greater than the demand, although in this respect we compare favorably with some other countries. In Germany the proportion of medical men has become so high that the average graduate has to wait some ten years before he succeeds in attaining an independent practice. In France the proposal has recently been made that all medical men on attaining the age of 65 years should be compulsorily retired, they being treated as crumbling monuments. The economic problem is becoming increasingly anxious. And yet, after all, to the man of scientific mind, even when his own personal problem of earning a living is successfully solved, this is only the working foundation of his career.

Each generation of medical graduates differs from its predecessors. Until the middle of the nineteenth century, and later, every qualified practitioner was regarded as a completely equipped medical unit, a walking compendium of knowledge, able to attack any problem presented to him by his trustful patients. But since those days of the so-called all-round man, not only has the pace quickened but the load to be carried has become heavier.

The first stage of specialism in modern clinical work was when general or major medicine diverged from general or major surgery.

The Specialties

The specialties within the medical profession are steadily increasing. The laboratory worker, the biochemist, the radiologist, the pharmacologist and others now perform work that is indispensable to the clinician, who has neither the special knowledge, the instrumental equipment nor the technical dexterity requisite for carrying out such observations. Secondly, there are the clinical specialists, who confine their activities to one special organ, or to one special aperture of the body. Their field is sometimes so restricted that they frankly admit being incapable of dealing with ailments outside it. Imagine a modern ophthalmologist supervising an obstetric case or a dermatologist dealing with a compound fracture. And the gallant general practitioner is expected by the public to deal successfully with all such cases. Nevertheless we need the skilled ophthalmologist and the expert dermatologist.

Specialism is advantageous, but in modern medical specialism there are dangers. One is the tendency of the specialist to lose the proper perspective of the patient as a whole. Another is the difficulty of keeping open the lines of communication between specialist and general practitioner. These lines daily become longer and more tortuous. When the vocabulary of any specialty becomes unintelligible to the average medical intelligence, it is in danger of losing its usefulness.

There are two kinds of specialists: the real and the false. Of the pseudospecialists there are examples to be found within the medical profession itself and a still more luxuriant crop of unashamed quacks outside it. He extends his practice mainly by astute canvassing. He has been deservedly pilloried by candid novelists. The pseudospecialist, greedy of notoriety and financial gain, is neglectful of ethical standards and sometimes actually dishonest. We are unhappily familiar with the blatant commercially minded consultoid who performs unnecessary operations on his richer patients for purposes of revenue and on his poorer ones in order to improve his technic. Sometimes he operates in order to accumulate and publish statistics demonstrating his own preeminent skill.

The true specialist is a man possessed of natural aptitude who, after intense training on special materials, sometimes necessitating dexterity in the manipulation of complicated apparatus, gradually attains to such a degree of knowledge and skill that he is deservedly recognized as a guide in difficult and doubtful problems. We have the good fortune to possess many such men.

How are we to recognize the true expert? He has characteristics by which he can be recognized. We observe the readiness with which he submits his results to control, criticism and reobservation by his colleagues. He records his negative results or failures as scrupulously as his successes. He avoids quoting so-called percentages when dealing with short series of figures. The pseudo-expert who has had four or five successful cases claims "100 per cent"

of successes. No one should speak of a percentage until he has had at least a hundred cases from which to quote.

What will be the future of medicine and of specialism? Every medical practitioner must remain a student to the end of his professional career. The day that a medical man ceases to learn, that is the day on which he should retire from practice.

The Future of Medicine

Some practitioners may for a time succeed in remaining up to date, but after years of busy practice many of us would make a poor show at a professional examination, in competition with our juniors, or even with some of our own pupils. The standard of knowledge of the general practitioner of today often surpasses the peak of certain specialists twenty-five years ago.

It may seem impracticable to make all doctors attend from time to time graduate courses in medicine, surgery and therapeutics. Some of the best men in the profession do so. It is encouraging that a program of this sort has recently been presented by the Ministry of Health as a gift to general practitioners wise enough to take advantage of it. But so long as graduate courses are optional and not compulsory it is chiefly the best type of practitioner who will attend them, while the more obsolescent types will continue to plod along the old roads, obstructing the speedier models which overtake them on the journey.

The family doctor who studies not only the disease but also the patient, who knows his patient's personal circumstances and constitutional tendencies, can never be replaced by the red-tape government official. His level of scientific culture will continue to rise and his functions will become not less but more important. To him it will fall to make the clinical application of scientific advances in the prevention and treatment of disease.

True specialism is essential to the progress of scientific medicine. The specialist of the future, with his superior skill in a restricted field, may expect to continue to be paid on a somewhat higher scale than the general practitioner, but not disproportionately high. This discrepancy will tend to diminish as the specialist finds himself in company with his fellow workers, becoming a cog in the complicated machinery of modern social life.

The leaders of the medical profession in the future will not be drawn almost exclusively, as at present, from its professorial and specialist members. The cultured general practitioner will come increasingly to the front. He will be the natural leader in every health campaign. He will represent his colleagues and his patients. He will defend their interests with a greater understanding than that of the academic members who now so largely comprise most of our official and deliberative assemblies.

THE DISCOVERY OF HENRY PLUMMER

In the year 1900 Dr. William J. Mayo [1] was called to Racine, Minn., in consultation with Dr. Albert Plummer to see a patient. Dr. Mayo drove the twenty miles from Rochester to Racine to find Dr. Plummer ill in bed. His son Henry, however, who had recently graduated, was in practice with his father and gladly went along to see the patient. The interesting story of this consultation is related here almost entirely in Dr. Mayo's own words. It was arranged, he said, that "I should leave my team of horses and ride the seven miles with Henry, who came out carrying a microscope. During the ride Henry talked to me about the blood, and he had an extraordinary amount of information about its composition, its characteristics and function, much of which I realized was not to be found in print at that time.

"The case we were to see was one of leukemia, of the type at that time called aleukemic leukemia; it is now designated leukopenic leukemia. Henry took a drop of blood from the ear of the patient, put it under the microscope and demonstrated the findings to me. He called in the hired man and a member of the family and took blood from each of them and under the microscope contrasted it with the blood of the patient for my information. On the way back he continued to talk about the blood, and spoke also of his interest in the thyroid gland.

"When I got home that night I told my brother that Dr. Plummer had a son in Racine who certainly knew more about the blood, at least, than any one I had ever met. I thought he was an extraordinary young man, and I believed we ought to try to bring him here and add him to the staff to bring our laboratories up to date. I wrote young Dr. Plummer and asked him to come up to talk with us. He came, we went over the situation, and he came on the permanent staff early in the year 1901.

"Henry took charge of the laboratories, and as a result of his efforts in a few months we possessed as good laboratories, I believe, as far as relation to clinical medicine was concerned, as were to be found elsewhere. In developing the laboratories he always kept the patient in mind. He used scientific apparatus not to take the place of clinical observation but to aid and verify.

1. Mayo, W. J.: The Work of Dr. Henry S. Plummer, Proc. Staff Meet., Mayo Clin. 13: 417 (July 6) 1938.

"I remember well that Dr. Charlie and I had been greatly impressed with the x-rays and such related mechanisms as were available at that early date, and we had acquired a rather imposing electrical machine. No one knew just what it could do, but it was thought to have some important diagnostic value. Unfortunately machines of this type were sometimes being used by charlatans to impress patients and for that reason we had all the connections of the machine which could be used for spectacular action pulled out and replaced with wooden pegs. We showed this machine to Henry, who was much amused. As he had developed the clinical laboratories, so he took over the x-ray work, and to the day of his death he carried the scars of x-ray burns on his hands.

"In 1889, when St. Mary's Hospital was first opened, in one of the earliest operative cases there was the largest thyroid tumor I have ever seen. The patient, a Scotchman aged about 62, lived near Racine, the home of the Plummer family. The patient had great difficulty in breathing and I knew that, whatever happened, the tumor must come out. While the patient made a good recovery, this was the beginning and end of my work in the goiter field.

"Henry Plummer as a boy knew this patient while at Racine and was familiar with the details of the case. It made such an impression on his mind that he became interested in the thyroid gland and in his college course followed the cases of thyroid disease in the dissecting room and the experimental laboratories. He remained intensely interested in the subject of the thyroid all his life.

"When Henry joined the staff, he was at once struck with the whole question of the purpose of the thyroid gland, its secretion, and its relation to health and disease. He made a special study of disturbances of function of the thyroid and cleared up many of the previously confusing ideas on the subject of thyroid disease. His studies on the effect of iodine in the preoperative treatment of exophthalmic goiter led to an immediate reduction of the operative mortality in this disease to less than 1 per cent, and the necessity for multiple stage operations was almost eliminated. This elucidation of the role of iodine in the treatment of exophthalmic goiter ranks among the great contributions to medicine.

"The many papers Henry Plummer wrote showed the progressive bent of his mind. He assiduously attended meetings of medical societies for the purpose of gaining information as well as to contribute. Always he concentrated on the fundamentals, the blood, the circulation, the heart, the kidneys and their relationship to the thyroid gland and other glands of internal secretion. Look over the bibliography of his scientific publications. Each article was carefully prepared; each carried the work discussed a step further. For thirty-six years there was a continuous development of the subject to which he gave his life.

"In 1899, as chairman of the Section on Surgery of the American Medical Association, I had written my address on esophageal stenosis. In one case of a different type, the obstruction was almost complete, yet there was no history of a cause. I had made a gastrostomy and had discovered that I was able to pass a sound up from below. Henry took over the case, developed the theory of cardiospasm, brought about dilatation of the stricture by the use of esophageal sounds, and cured the patient. He continued in this field with the greatest enthusiasm and developed mechanical methods of removing foreign bodies from the esophagus. From this phase of the study he passed to the investigation of diverticula of the esophagus. He developed bronchoscopy for the removal of foreign bodies in the bronchi, accomplished dilation of bronchial strictures, and worked out the method of diagnosing disease conditions of the lung by securing specimens of involved lung tissue for microscopic examination. His study of oxygen requirements led to the building of airtight glass oxygen chambers. These rooms, which preceded the oxygen tents commonly employed today, are still in use. In this field he achieved extraordinary results. Henry was a genius in mechanical detail. The first Mayo Clinic building, begun in 1912, was essentially his work, in which the architects gratefully acknowledged his leadership. The present clinic building connected with the old is his monument.

"Loved by his confrères and respected by the learned men of the profession the world over, Henry S. Plummer passed away Dec. 31, 1936, at the age of 62. When stricken with bulbar paralysis he recognized what it was and asked to have the family summoned, saying that in an hour he would be unconscious. As long as that intelligence which had carried him through life was permitted to function, he traced the progress of this last illness.

"The life of Dr. Henry S. Plummer was devoted to the welfare of mankind."

How to Become a Diagnostician

The high-developed clinician examines his patients carefully and minutely, he recalls the course of disease in past patients and becomes a prophet of the future course of disease in each new patient; he knows from experience the possibilities and the failures of treatment; he is cool and collected; he plans a campaign of therapy and pursues it day by day, not easily driven from his plan unless new conditions develop. . . . Persistently experience and knowledge are increased; eventually by reason of attainment in experience and knowledge increasingly the physician is sought by other physicians for help in solving their problems; he has become a consultant.—Christian, Henry A.: The Lure of Medicine, *Virginia M. Monthly* **65**:515 (Sept.) 1938.

Medical College News

Medical schools, hospitals and individuals will confer a favor by sending to these headquarters original contributions, reviews and news items to be considered for publication in the Student Section.

Interns' Contest in Mahoning County, Ohio

Four interns presented case reports before the Mahoning County Medical Society in Youngstown, Ohio, June 21, at the annual Interns Contest sponsored by the society. The first prize of $15 was awarded to Dr. Densmore Thomas for his paper on "Trichinosis" and the second prize of $10 to Dr. Donald A. Miller for his report of a case of "Stab Wound to the Left Side of the Chest." The prizes were awarded in consideration of the completeness of the work-up of the case, the significance and teaching value of the case itself, and the manner of presentation. The four papers were so equally interesting that the decision of the five judges was reached on the delivery alone.

Memorial in Africa to Noguchi and Young

A memorial to the late Drs. Hideyo Noguchi and William Alexander Young was formally unveiled by Sir Arnold Hodson at Akkra, Gold Coast, Africa, April 2. A representative gathering of the people of Akkra was present at the ceremony. Before the unveiling Dr. David Duff, director of medical services for the Gold Coast, gave an account of the work of these two medical martyrs. In addition to this memorial a brass plate, suitably inscribed, will shortly be placed in the room of the Medical Research Institute at Akkra, where Noguchi and Young conducted their yellow fever studies. Noguchi had gone to the Gold Coast in British West Africa as representative of the Rockefeller Institute for Medical Research, New York, to complete researches on yellow fever, and he died of that disease at Akkra, May 21, 1928. He was born in Japan and graduated in medicine at Tokyo Imperial University in 1897. Subsequently he worked in the University of Pennsylvania. Young, also one of a scientific party sent to Akkra by the Rockefeller Institute for Medical Research, died there May 29, 1928, of yellow fever. Dr. Young was of Scotch descent and received his medical education in England.

Fellowships Available in Chile

Two fellowships will be available next year to American students for study at the special January session of the University of Chile. These fellowships are offered by the Chilean government and include tuition, 900 Chilean pesos for living expenses, and a pass on the Chilean railroads. In addition the Carnegie Endowment for International Peace has granted $500 to each fellowship to cover traveling expenses to and from Chile. Preference is given to candidates who have had at least a year of graduate work. Applications are available at the Institute of International Education, 2 West 45th Street, New York City.

Hunterian Professorship Awarded to Canadian

The Hunterian professorship in the Royal College of Surgeons of England has been awarded to Dr. Donald W. G. Murray of Toronto. This is the second time this award has been given to a Canadian professor, the other occasion being in 1924, when Dr. William E. Gallie of Toronto was so honored. The distinction comes to Dr. Murray as a result of his work on heparin, which has been done in conjunction with Dr. Charles H. Best, professor of physiology of the University of Toronto. Dr. Murray will give his lecture in London, England, next year.

Fiftieth Anniversary of Marine Biological Laboratory

The fiftieth anniversary of the Marine Biological Laboratory, Woods Hole, Mass., is being celebrated this year, according to *Science*. A portrait of Mr. Charles R. Crane, New York, who was largely responsible for the growth of the institution, was presented at an informal meeting to celebrate the semicentennial of the laboratory. Mr. Crane was president of the board of trustees from 1902 until 1925; he gave a completely equipped laboratory building in 1914 and later a large sum for an endowment fund. The first building was opened for the use of seven investigators and eight students in the summer of 1888, with Prof. C. O. Whitman, Chicago, as director. The attendance is now more than 500. To the original building, still used for investigation and research, have been added other wooden buildings and a large brick laboratory containing a library, research rooms equipped with running fresh and salt water, chemical and apparatus rooms, an x-ray installation and a large auditorium. A statement of Professor Whitman expresses the aim of the laboratory: "The Marine Biological Laboratory attaches itself to no single institution but holds itself rigidly to the impartial function of serving all on the same terms. . . . The whole policy is national in spirit and scope. The laboratory exists in the interests of biology at large." Recent changes in the staff include the appointment of William W. Ballard, Ph.D., assistant professor of zoology and anatomy, Dartmouth College, Hanover, N. H., and Douglas M. Whitaker, Ph.D., professor of zoology, Stanford University, California, to succeed Lester G. Barth, Ph.D., assistant professor of zoology, Columbia University, and Charles Packard, Ph.D., assistant professor of zoology at Columbia, who resigned from the embryology staff.

Faculty Changes at Oklahoma

The University of Oklahoma School of Medicine, Oklahoma City, has conferred the title of emeritus professor on Dr. Edmund S. Ferguson, professor of ophthalmology; Dr. William M. Taylor, professor of pediatrics, and Dr. John F. Kuhn, professor of gynecology. Dr. Leslie M. Westfall, professor of clinical ophthalmology, succeeds Dr. Ferguson; Dr. Clark H. Hall, associate professor of pediatrics, succeeds Dr. Taylor, and Dr. Grider Penick, associate professor of gynecology, succeeds Dr. Kuhn.

Vermont Now Requires Three Years for Admission

The College of Medicine of the University of Vermont has adopted requirement of three years of college work as minimum for admission. This will take effect next fall.

Miss Helena McMillan Retires

Miss Helena McMillan, a leader in hospital and nursing education and for thirty-five years head of the School of Nursing of the Presbyterian Hospital of Chicago, has announced her retirement as director of that school effective in October. Miss McMillan's work has not been confined to nursing; she has been interested also in hospital administration and the development of better care of the sick in the home as well as in the hospital. The *Journal of the American Hospital Association* points out that she is perhaps the only

person living who participated in the second annual convention of the American Hospital Association in Cleveland, at which time Miss McMillan presented a paper on "The Relationship Which Should Exist Between the Superintendent of the Hospital and the Superintendent of Nurses." Miss McMillan was at that time superintendent of the School of Nurses of the Lakeside Hospital in Cleveland.

Ohio Personals

Dr. Alec Laidlaw Phimister has resigned as demonstrator in medicine at Western Reserve University School of Medicine in Cleveland to enter the practice of medicine in London, England. Dr. Kenton R. Phelps, graduate of Western Reserve University School of Medicine in 1935, was appointed a resident in neurologic and cardiac surgery at the University Hospitals, Cleveland, beginning July 1, 1938. Dr. Carl H. Lenhart, director of surgery in the University Hospitals of Cleveland, has been elected president of the Cleveland Medical Library Association. In addition to being professor of surgery at Western Reserve University School of Medicine, Dr. Lenhart has been "directing librarian" for eighteen years.

Alumni Reunion in Ann Arbor, Mich.

A reunion of the alumni of the University of Michigan Medical School and of the former staff members and interns of the University Hospital, Ann Arbor, was to be held September 29-October 1. Among other speakers were the following:

Dr. Reuben Peterson, Duxbury, Mass., Landmarks in the History of the University of Michigan Medical School and Its Hospital.
Dr. Cyrus C. Sturgis, Ann Arbor, A Résumé of Eleven Years' Experience in Hematology at the Simpson Memorial Institute.
Dr. Donald D. Van Slyke, New York, The Physiology of Renal Excretion.
Dr. Norman F. Miller, Ann Arbor, Common Lesions of the Cervix.
Dr. Ward J. MacNeal, New York, Bacteriophages as Aids in Dealing with Infections.
Dr. Carl E. Badgley, Ann Arbor, A Study of the Causes and Methods of Prevention of Nonunion of Fractures of the Shaft of the Long Bones.
Dr. Walter Bauer, Boston, The Physiology of Normal Joints and Its Relation to Joint Disease.
Bradley M. Patten, Ph.D., Ann Arbor, The First Heart Beats and the Beginning of the Circulation of Blood as Shown by Micro Moving Pictures of Living Embryos.
Dr. Carl V. Weller, Ann Arbor, The Intrinsic Factor in the Etiology of Malignancy: Inheritance of Retinoblastoma.
Dr. Joseph Brennemann, Chicago, Abdominal Pain in Children.
Dr. Hugo A. Freund, Detroit, Renal Ischemia and Vascular Hypertension Associated with Coarctation of the Aorta.
Dr. Max M. Peet, Ann Arbor, Results of Splanchnectomy for Hypertension.
Dr. Hugh Cabot, Rochester, Minn., Intravenous Urography: Its Place in General Medical and Surgical Diagnosis.
Dr. Francis E. Senear, Chicago, The Serologic Diagnosis of Syphilis.
Dr. Frederick A. Coller, Ann Arbor, Physiology and Chemistry in Surgery.
Dr. Frank N. Wilson, Ann Arbor, The Differential Diagnosis of Coronary Occlusion.
Dr. Charles W. Edmunds, Ann Arbor, The Problem of Drug Addiction.
Dr. Warren T. Vaughan, Richmond, Va., Tissue Tension Studies in Clinical Allergy and Experimental Anaphylaxis.
Dr. James B. Herrick, Chicago, Acute Endocarditis.
Dr. Louis H. Newburgh, Ann Arbor, A New Interpretation of Diabetes Mellitus in Middle-Aged Obese Persons.
Dr. Perrin H. Long, Baltimore, Further Observations on the Experimental and Clinical Use of Sulfanilamide.
Dr. Frederic M. Loomis, Oakland, Calif., The Third Component: The Relationship Between Them.
Dr. Hiram Winnett Orr, Lincoln, Neb., Methods for the Prevention and Cure of Septicemia Following Injuries and Surgical Operations.
Dr. Udo J. Wile, Ann Arbor, Sex Hormone Studies in Acne. The Urinary Excretion of Androgenic and Estrogenic Substances.

Dr. Frederick G. Novy, dean emeritus of the medical school, was the speaker at the banquet in the Intramural Sports Building. Dr. Bauer and Dr. Richard H. Freyberg, Ann Arbor, conducted a round table discussion on arthritis at a luncheon September 29. The following day a symposium on poliomyelitis was presented at luncheon. The reunion was to be concluded October 1 at the opening convocation of the medical school when Dr. Francis Peyton Rous of the Rockefeller Institute for Medical Research, New York, was the speaker.

Aid for Study of Vascular Problems

The Taylor Instrument Companies, Rochester, N. Y., gave $5,000 to further investigation in the field of vascular problems by Drs. Mont R. Reid and Louis G. Herrmann of Cincinnati. This gift will be placed in the Pavaex Appreciation Fund. According to the *Journal of Medicine*, Drs. Herrmann and Reid have given years of altruistic endeavor in their development of passive vascular exercise therapy, and the Taylor Instrument Companies has manufactured the instrument without financial profit. Dr. Reid is head of the department of surgery, and Dr. Herrmann is assistant professor of surgery and director of the vascular clinics at the Cincinnati General Hospital.

Promotions at Vanderbilt

The following promotions at Vanderbilt University School of Medicine, Nashville, have been approved by the board of trustees: Dr. Samuel M. Bloomstein to professor of clinical pediatrics, Dr. Leonard W. Edwards to associate professor of clinical surgery, Dr. Rudolph H. Kampmeier to associate professor of medicine, Dr. Ralph M. Larsen to assistant professor of surgery and anatomy, and Dr. Guy Sydney McClellan to assistant professor of obstetrics and gynecology.

Aid for Pellagra Investigation

The Markle Foundation, New York City, has appropriated $14,000 to support the investigations of pellagra for a two year period now being conducted by Dr. Tom D. Spies, associate professor of medicine at the University of Cincinnati College of Medicine. The Josiah Macy Jr. Foundation gave $4,500 to support these investigations until next February.

Prizes for Students at Maryland

A prize of $25 is given each year by Mrs. Abram B. Gaither, as a memorial to her late husband, to the student in the senior class at the University of Maryland School of Medicine who does the best work in genito-urinary surgery.

Another annual prize of $25 has been established by Mrs. S. M. Shoemaker and Mrs. B. F. Johnston as a memorial to Samuel M. Shoemaker for the best essay on "Milk in Relation to Public Health," written by a student in the senior class.

Pathologists Appointed at Long Island

Dr. Caspar G. Burn, assistant professor of pathology at Yale University School of Medicine, New Haven, Conn., has been appointed associate professor of pathology at Long Island College of Medicine. Dr. Burn graduated from Yale in 1930. Dr. John Musser Pearce, recently on the staff of the Rockefeller Institute for Medical Research, Princeton, N. J., has been appointed instructor in pathology.

Gift for Gynecology at Pennsylvania

The University of Pennsylvania School of Medicine has received $50,000 from the estate of Dr. William C. Goodell, who died in 1918. The bequest is to establish the William Goodell chair in gynecology, it was reported.